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PREFACE

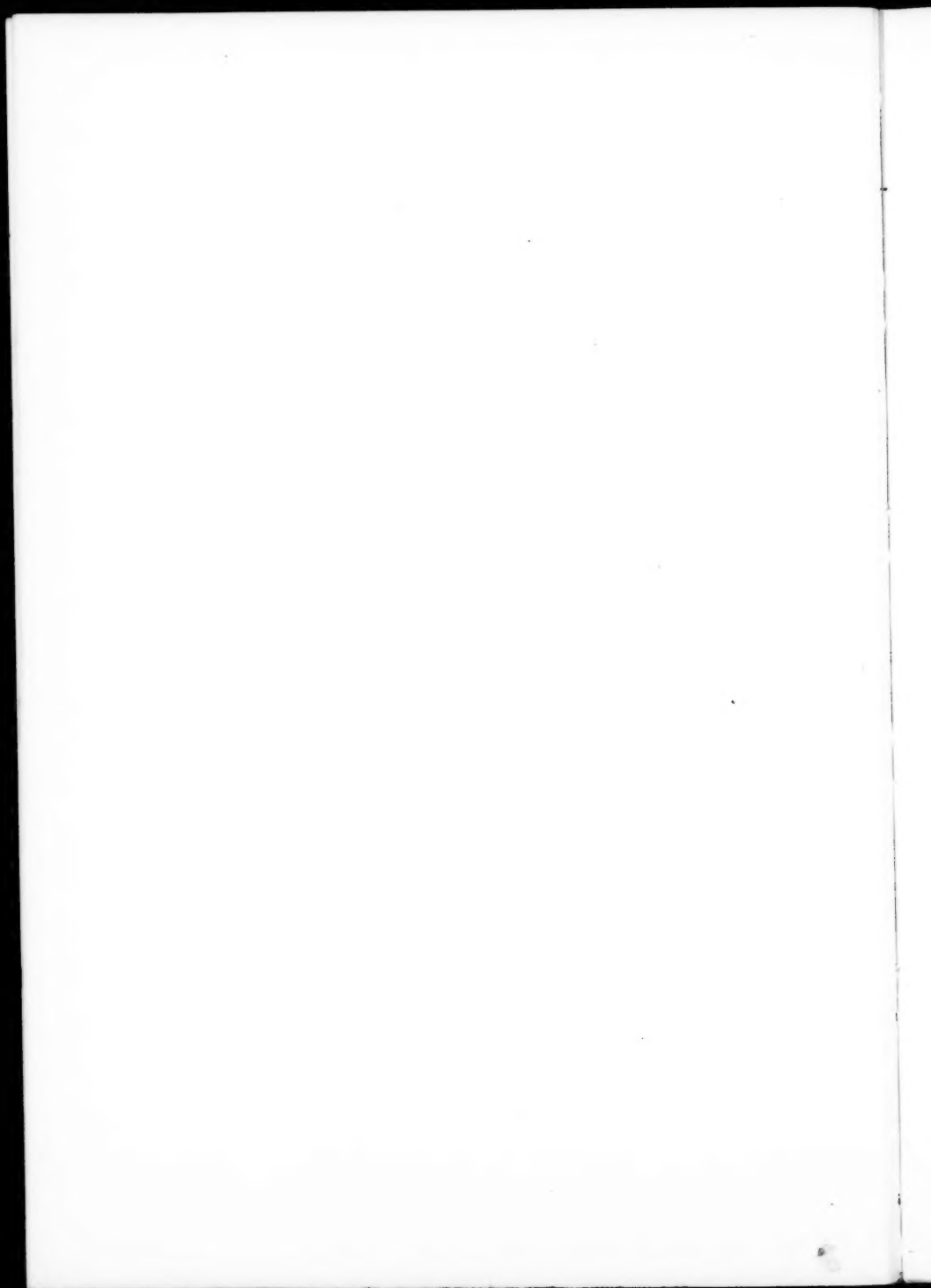
The present volume of the *Annual Review of Physiology* surpasses in point of length all its recent predecessors. All the promised chapters have been received and included. Even with the extensive editorial extirpation—and again we wish to express to our authors and to the workers whose contributions were thus not mentioned our sincere regrets for the necessity of taking this action—the bulk of the volume seriously strained the financial resources of the enterprise.

The continuing growth of physiological activity and of the number of workers involved therein has begun to tax the ability of the five member Editorial Committee to maintain adequate contact with such activity. Accordingly, the membership has been increased to seven. With the retirement of Dr. M. H. Jacobs, whom we wish to thank for his long and valuable service, the Committee has been brought to full strength by the appointment of Dr. J. P. Baumberger, Dr. J. Field, and Dr. W. F. Hamilton.

We present in this volume the first of a series of chapters on comparative physiology, the first of which, written by Dr. C. A. G. Wiersma, deals with invertebrate muscle. This will be followed by chapters on various aspects of the general field with recurrent treatment of each at intervals of perhaps five years. Among the lower forms anatomical and physiological arrangements exist which not only often lend themselves much better than do those of common laboratory animals to the investigation of certain processes, but which sometimes open new vistas of thought, breaking through the provincialism of purely mammalian physiology. Such are the considerations which have led us to this new venture.

A development which will soon be reflected in the content of the *Review* is the inauguration of the National Science Foundation. Although the federal government has through various agencies been supporting fundamental studies in physiology and allied sciences, this has been done almost entirely as an adjunct of studies primarily directed at the solution of specific medical and military problems. The establishment of the Foundation now recognizes directly that the advancement of basic scientific knowledge is a matter of national interest. Under the leadership of men who have themselves contributed actively in their fields, the Foundation is developing policies for support of research recognizing that full freedom in its planning and conduct is the best assurance of fruitful effort. We are confident that with such policies the Foundation will become a dominant influence in the development of American science.

J.P.B.	R.F.P.
J.F.	M.B.V.
J.F.F.	J.M.C.
W.F.H.	A.C.G.
F.C.M.	V.E.H.



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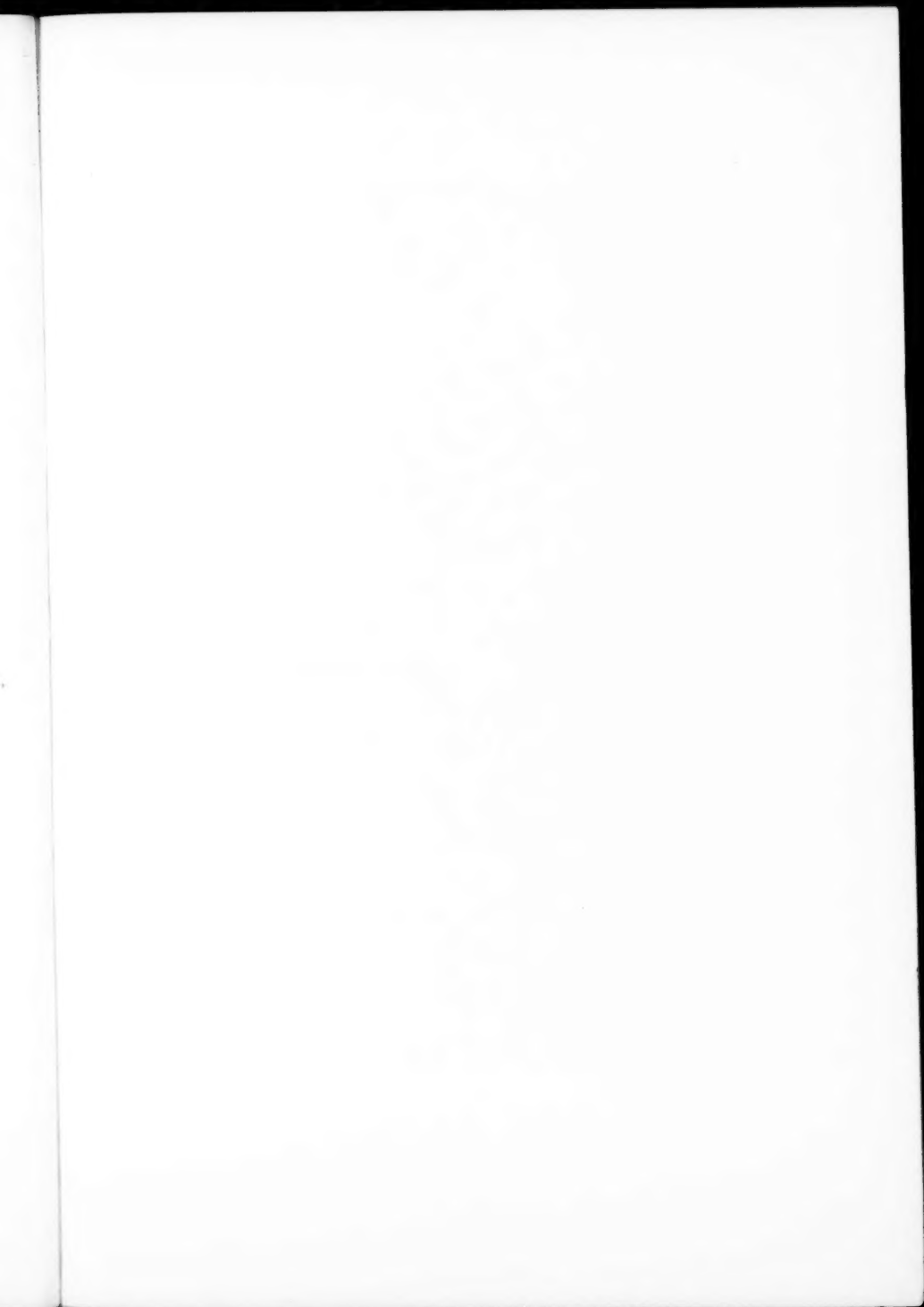
page 336, reference 44: *for* (1949), *read* (1948)

page 355, line 20: *for* lightly, *read* firmly

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R. W. GERARD, PH.D., M.D.

PREFATORY CHAPTER

THE ORGANIZATION OF SCIENCE

BY R. W. GERARD

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Once upon a time, science was the hobby of amateurs. These harmless, if eccentric, individuals, blessed by fortune or the patronage of nobility with the requisite leisure and materials, puttered about the simpler phenomena of nature, irregularly reported their findings to one another by letter or *via* itinerant scholar, enjoyed their private satisfactions, and magnificently ignored and were ignored by the outer world. They did not live in ivory towers, but often enough in battlemented ones of cold stone. Now and then some useful result emerged. Archimedes presumably did decide whether the crown was adulterated with lead and did improve the bombards of the day, as did Leonardo, in turn, in his time. Now and then some vagrant wind ruffled the grasses, as new ideas impinged on old beliefs; Paracelsus in one way and Galileo in another publicized themselves enough to disturb the medieval mind. But science and scientists remained on the whole unimportant and obscure.

The explosion of experiment and rationalism in the early seventeenth century generated pressures which changed all of that. Observations required apparatus and clamored for audience. Scientific groups and societies, formal laboratories, and regular publications crystallized from the earlier amorphous activities. Organization supplemented spontaneity, and in time science became an institution of society, an organ which, perhaps like the human cerebrum, followed its own exponential law of orthogenic growth and, with an accelerating flow of inventions, worried and molded the entire body politic. Today most of our ways of life and some of our ways of thought stem from science; and, today, the nature and future of science are inseparably and irreversibly bound with those of the larger social group.

In the seventeenth century came mechanics and gravitation and the circulation of the blood, the telescope and microscope and vacuum pump, the slide rule and graph and calculus. In that astounding period came the break with authoritarianism, the exaltation of objective evidence, the formulation of the combination of experiment and reason which dominates scientific method today; came into being the Royal Society in England and its continental sisters in Italy, France, and Germany. And at that time came Bacon's inductive "histories" and "instances" and his prophetic "Salomon's House" to gather "the matter . . . from natural history and mechanical experiments and lay it up . . . in the understanding altered and digested," as the bee gathers material from the flowers but transforms it by a power of its own. To do all this, moreover, "that human life be endowed with new discoveries and powers"; the "true and lawful goal of the sciences."

The "riches" of the house of Salomon consisted in a series of laboratories devoted to all conceivable subjects of experimental research, with facilities of utopian perfection—laboratories beneath the ground, observatories on high towers upon mountain peaks; all apparatus for physiological experiments; botanical and zoological experiment stations in the fullest sense of the word; places for dissection, chemico-pharmacological and physical laboratories; special laboratories for the study of heat, of optics, of sound, of engineering problems, all sketched in a completeness which the twentieth century has not reached, but along lines toward which scientific progress has been advancing. All this is put in charge of a hierarchy of scientists, the Merchants of Light, who are to bring news from foreign lands, the Depredators who ransack books for scientific facts, the Mystery Men who collect experiments in the mechanical arts, the Pioneers who try new experiments, the Compilers who tabulate the results, the Dowery men who try to derive practical benefit, the Lamps who direct new experiments, the Inoculators who try these, the Interpreters of nature who "raise . . . discoveries into greater observations, axioms, aphorisms" (1, p. 43).

The method of compilation and digestion did not, for three centuries, occupy a major role in scientific discovery; but it is now perhaps on the threshold of doing so. Nor did group investigation, by a co-operating team of specialists, amount to much, but it is now upon us. And the social uses of science, far from the spotlight of research or political attention, have, increasingly since the industrial revolution of the eighteenth century, moved to front center on the stage of civilization. Science was delivered from the womb of time one-third of a millennium ago as a lusty infant. It has grown since then, not only in the body of knowledge it encompasses and of workers devoted to it, but also in its scope and techniques and in its internal and external relations. If science is, as I have called it (2), the autocatalyst of social evolution and if science is an integral part of the social organism [or epiorganism (3)], it would be well to examine some of these changes. Nor is this task unrelated to physiology as such, for biology is the study of organism and physiology could be called the ecology of cells in the body, as sociology could be called the physiology of society.

CHANGING SCIENCE

First, some perhaps unproven generalizations. There are striking uniformities in the trends of various segments of science; some having to do with emphasis on content deserve initial attention. Each discipline begins in a descriptive or classificatory manner. The subjects or entitles of interest to it, the nouns of its language, are identified, described, tabulated, and ordered. This is the taxonomic stage, whether dealing with pure compounds in chemistry, minerals in geology, species in botany, structures in anatomy, or specific functions in physiology. Next is the static or structural stage, during which relations as quantitative as possible are established between these entities, and verbs of state are introduced. Pythagoras' law, Ohm's law, Boyle's law, Bell's law, and Starling's law are fruits of such activity. Then come the dynamic stage and the verbs of change, when variations in time, space, and other conditions are introduced and the shift in relations exam-

ined. Integers preceded infinitesimals; electrostatics, electrodynamics; molecular structure, reaction rates; and the architecture of bodies, their action. Finally, with the holistic stage, the language is completed, the units in their variable relations are returned to the whole, the Gestalt is recognized, the planet or the organism returns to the center of focus.

But this is too simple, for these stages apply not to each science but to each level within it. The natural entities examined by science are not ultimate indivisible units but are built of units which are themselves entities built of lesser units, often in a long regression. Man first grapples nature at a level dictated by the dimensions of his unaided senses, then pushes his way up or down through the layers—the astronomer to supergalaxies, the physicist to subnucleons—as instrumental aids enrich his senses and insight orders data. At the present rate of advance, at least in biology, scientists are moving a level per generation. Before this century, the organism had been dissected, structurally and functionally, to the organ level; during the first half of the 1900's, the analysis swept on to the tissue, then to the cell; and during the second half, it is already pushing on to the organelle, particle, and molecule.

Organ systems do not go out of bounds, however, when organelles come in. Each level advances through its own stages, development only being accelerated by the light reflected from other levels. Homeostasis is a holistic concept at the level of the organism. It gained in richness and precision from Claude Bernard to Cannon as the contributory organ systems were laid bare, as the actions of the liver and parathyroid and depressor nerve were recognized. It continues to gain as thiamine and cytochrome and cortisone enter the picture, and will so continue as ever more intimate mechanisms of membrane permeability, and enzyme action, and micellar architecture and gene reduplication are revealed. Similarly, behavior of the whole organism was studied for long at the descriptive level, while the nervous system was probed to nuclei and neurones and synapses, to action spikes and ion movements. Today, as these elements are recombined, the properties of neurone nets and potential fields and metabolic rhythms give more than promise of an understanding of behavior dynamics.

It is only when attention remains too long fixed on one stage at one level that workers there develop the pessimistic feeling of the great days lying behind them. (Youngsters working at a new level tend to be intolerant of their seniors continuing at an older one, and oldsters lament the lack of perspective of their juniors, both groups being mostly unaware of what is really happening.) Such a condition probably provoked Michaelson's comment that the future of physics was limited to pushing further to the right of the decimal point. It certainly led to Barklay's plaint (4, p. 86):

Gentlemen, while carrying on your work in the dissecting-room, beware of making anatomical discoveries, and above all beware of rushing with them into print. Our precursors have left us little to discover. You may perhaps fall in with a trifling supernumerary muscle or a tendon, a slight branchlet of an artery, or perhaps a

minute stray twig of a nerve—that will be all. But beware! Publish the fact, and the chances are ten to one that you have been forestalled long ago. Anatomy may be likened to a harvest field. First come the reapers who, entering on untrodden ground, cut down great stores of corn from all sides of them. These were the earliest anatomists of modern Europe, such as Vesalius, Fallopius, Malpighi and Harvey. Then come the gleaners, all gather up ears enough from the bare ridges to make a few loaves of bread. Such were the anatomists of last century—Winslow, Vicq d'Azyr, Camper, Hunter and the two Monros. Last of all come the geese, who still contrive to pick up a few grains scattered here and there among the stubble, and waddle home in the evening, poor things, cackling with joy because of their success. Gentlemen, we are the geese.

Such psychological factors may be related to a uniform behavior pattern among scientists. In any event, if a scientist shifts his field of interest after his career is well under way, the move is almost invariably toward the more complex level or the applied. The pure mathematician turns to theoretical physics or statistics (or philosophy); the physicist, to physical chemistry or biophysics; the chemist, to biochemistry or industry. Biochemists penetrate cytology and physiology; physiologists, the clinical disciplines and psychology; and so around the wheel of knowledge. The great who swim against this current are few; it is easier to bring a rigorous background into a less rigorous area than the reverse. (Helmholtz, who went from medicine through physiology to physics—but with strong mathematics from the start—is, perhaps, the outstanding example. Michaelis is a more recent one.) But our concern now is not with the men or their movements; it is with the consequences to science. There is some sort of law of mental action and reaction, too; so, as scientists move clockwise, the sciences move counterclockwise. Chemists and physicists become physiologists and help make physiology more biochemical and biophysical; physiologists become internists and psychologists and help make their new disciplines more physiological. Such changes are surely among the important ones that we identify as progress (5).

So much for content; changes in procedures are no less striking. Apparatus, as such, requires only mention; the chains from mercury manometer to strain gauge, from Haldane's gas analyser to Pauling's, from inductorium to thyatron, from colorimeter to spectrophotometer and counter, in general from the coarse and slow to the sensitive and rapid, are too well known to dwell upon. Yet, of themselves, these changes are in degree, not kind. The tale of one of the earliest demonstrations to the American Physiological Society has a contemporary ring to the neurophysiologist with a frog sciatic mounted retiringly in some crevasse among towering relay racks. The entire Society was comfortably gathered in his laboratory and Bowditch explained enthusiastically the strings and levers giving records on the drum—a time signal, a temperature record, stimulation, and many others. One line on the unfolding graph was, uniquely, quite irregular and some member (a proto-Carlson) demanded an explanation. "Oh, that," said Bowditch with obvious impatience, "is the cat."

What is important, and a change in kind, is that the users of instruments are increasingly not their masters. Once, any physiologist could tinker a kymograph into good behavior and even make or have one made in the shop in the basement. Few today dare open the crinkle-finish black boxes purchased from some "radio" firm, and, even of those who do, a small number indeed could carry on without the services of an expert electronics engineer. This may be unfortunate, but it is certainly inevitable. Not only do instrument societies flourish now, but a formal discipline of instrumentology is rapidly becoming established—indeed, becoming subdivided into new specialties (6)—so that a self-respecting physiology laboratory can hardly limp along with only (besides technicians) glass blower, mechanic, and electrical factotum.

The same theme, with variations, carries over from material tools to intellectual ones. Biological theory has been, on the whole, nonquantitative; but only in part is this because of the complexity and fuzziness of the presenting phenomena. It has needed as well, and is getting (7), new mathematical methods to solve the problems. Mathematical biologists are contributing powerfully in reaction chain theory, in population genetics, in the analysis of information and communication, even in statistical theory proper. And statisticians are advising biologists on, "The Design of Experiments" (8). Following Weaver's provocative analysis (9), mathematics early produced tools, as the calculus, to solve the "problems of simplicity" of classical physics and chemistry, epitomized in the two-variable problem. More recently, by statistical techniques of the probability kind, it has created tools to handle large groups of random events, as in thermodynamics, the "problems of disorganized complexity."

Many problems of biology (and sociology) are, however, matters of "organized complexity"—inherent in the nature of organism—and for these new methods are needed. Some are along orthodox lines of deductive mathematics, others smack strongly of Bacon's inductive proposals. A virtue of the high speed electronic calculators is that, lacking formal solutions, trial and error answers can be obtained by allowing many variables to range freely over possible values. The "operations analysis" teams of the past war handled many interrelated factors by pooling the knowledge (and imaginations) of an interdisciplinary group of scientists, often with brilliant success. (Incidentally, biologists, accustomed to multiple variables, were particularly effective.) The Chemical-Biological Coordinating Center, another war baby, is doing a more formal job of collecting, coding, and systematizing on punch cards the biological effects of chemical compounds. All are devices for obtaining empirical relations where insight and deduction have not found a path through the maze of multiple interdependent variables.

With probability elements introduced into the calculators, imagination may someday be built into machines (10); until then we must depend on creative insights of the individual human mind. But genius does not operate *in vacuo* and much can be done to feed it useful information. Even without a

brilliant closure, many important relationships would become apparent if the proper facts were marshaled in the proper array. Many periodic tables are lurking in the scientific tomes at this moment. As new compounds pour into Beilstein, as new physicochemical properties become tables in handbooks, as new biological structures are seen and processes identified, as the influence of one on the behavior of another is explored, the permutations multiply beyond the mere number, 10 billion, of neurones of a human nervous system. Perhaps the most important problem facing science today—and one well within the possibility of early solution, in contrast to the distantly envisaged one of obtaining “better” men or brains—is that of making useful the huge midden heaps of desiccated facts. Such agencies as the *Annual Reviews* help a little. Libraries are becoming museums by the sheer volume of volumes. Stored knowledge must again be made functional, and the sorts of mechanical and intellectual devices for achieving this are at hand or clearly envisioned (11). Printing was a necessary invention for the intricacies of modern thought; it is not a sufficient one.

Thus, in the making of observations, in the development of interpretations, and in the communication of information, we come against the problem of organization. Many do not like this. A considerable group of distinguished scientists has formed a “Society for Freedom in Science” to oppose the trend. Bureaucracy in science is a sitting duck for caricature and receives plenty of it, some delightfully ironical (12). But the tide would not stop for Canute nor the coasting freight car for the novice brakeman's foot and, like Margaret Fuller, we had better accept the universe. How much organization and of what sorts—these are more useful problems for attention.

Even the lone researcher obtains immeasurable help in his experiments from others, others who have purified his chemicals, fabricated his apparatus, pioneered his procedures. He may now get further help by sending samples away for bioassay or microanalysis or histologic preparation, and he must get outside help in obtaining radioactive materials. As instruments become more costly and the skills in using them more demanding, investigators will more and more “farm out” segments of their problems. A parallel exists in modern medical practice, the difficult case being a research problem and the physician, the investigator. He attacks his problem with all the relevant techniques to reach a successful answer, a correct diagnosis; but he does not attempt to apply them himself. Electrocardiograms, blood cholesterol values, roentgenograms, Rohrschach profiles, basal metabolic rates are obtained from men and laboratories specialized to make such measurements. Nor are the best of these mere service agencies; the roentgenologist or clinical physiologist may himself be busily creative in his own area of interest, exchanging some routine service for active support of his own research.

Further, these medical workers form teams; in hospitals or clinics or by simple association, under university or government or private auspices, for fees or salaries or nonmonetary benefits, they work together. In scientific

research also, where economic competition is minimal and the range and depth of desirable competence is maximal, men must work together.¹ The character of research teams is not fixed. Those involved may be together in one building or scattered in several cities; there may be a "boss" or a dynamic leader or a council of peers with fluctuating leadership; effort may be full time or consultatory, all on one problem or divided between many; work may be paid for in salaries or not (but must always be paid for in individual satisfactions); but on some basis or other scientists must co-operate.

What happens in the whole development of science . . . is the exploitation of such correlations and the multiplication of researches. . . . As each new substance or property or phenomenon is discovered, it becomes not only possible but obviously desirable to follow its variation under every kind of condition. So the bright area of knowledge ever spreads and, although the dark surface of ignorance is presumably decreasing, the perimeter of contact with the unknown also increases. Most of us are adding our little bit at a small segment of line. The lengthening line means a need of ever more workers and more facilities to do the work. That is why every field keeps growing and expanding—and universities go broke. . . .

But, by and large, . . . our work seems to me a good deal like the building of a termite nest. We are engaged in a collective job, some working in one gallery, some in another. The individual termites operate without any plan that we are able to divine. As one watches the termites at work building a nest, there appears to be utter confusion. Each rushes around, drops its excreta at some particular point, and rushes around some more. Nevertheless, as the edifice grows, the tunnels and galleries do connect, and the walls coming together from the two sides join perfectly (13).

Much is to be learned and invented for securing the full advantages of group effort while leaving a maximum of individual creativeness and satisfaction. But only the details will be unique to science, for this is the great challenge to civilization itself (14) and one which, at long last, is beginning to engage a full-muscled effort.

SCIENCE AND GOVERNMENT

It is significant that the first two past-presidential addresses to the American Physiological society dealt with the external relations of science, with governmental demands on physiologists (15), and with security and loyalty problems (16). On a more intimate note, the changing milieu was epitomized in three sentences in the first of these prefatory chapters (17).

In the first two decades of this century the professor spent the day making his own

¹ A simple check reveals the course of events in physiology over half a century. Volume 3 of the *American Journal of Physiology*, published in 1900, contained 30 articles in about 500 pages; Volume 158, published in 1949, contained over 250 articles in about 2000 pages. (Research reports have clearly become more terse.) But more striking than increase in volume is the increase in multiple authorship. In 1900, 70 per cent of the papers had a single author; in 1949, 24 per cent. Double authorship occurred 27 per cent of the time in 1900, 32 per cent in 1949; and triple authorship, 3 per cent and 32 per cent, respectively. Larger groups did not appear in 1900; but in 1949, 10 per cent of the papers had four authors and 2 per cent had still more.

physical measurements and chemical analyses. Then he went home, and a maid cooked the dinner and washed the dishes. Nowadays, it is the technician who makes the scientific measurements, and the professor washes the dishes after the dinner that has been cooked by his wife.

A proper discussion should include a full balance sheet of credits and debits, to science and to society, resulting from their growing organization and interdependence. This cannot be attempted here, the more so since portions of the problem have been considered in previous articles (18 to 21). There seems little doubt, if only on the Darwinian argument of survival, that the balance has been plus for society. Industry, war, government, daily living, demand ever more science, or at least its products; presumably it is useful. The doubts are on the other side; whether science will lose its soul in gaining the world. It bears repetition, however, that the increase in organization is an inexorable trend in evolution; our problem is to fight the diseases and enhance the uses of interrelatedness.

The great danger is authoritarianism and conformity. This can blight at any level, from the petty bookkeeping practices of too many governmental agencies to the national murder of the free pursuit of truth. The Lysenko story in Russia (22, 23) and the earlier distortions under Hitler (24, 25) deserve the most careful attention by scientists. Although these represent excesses under totalitarian police states, the anlagen of similar attitudes are clearly present in our own country (20). Anyone unaware of the threat, not only to science but to our military strength and our democratic traditions, of the distortion of legitimate security measures and loyalty tests into politically-inspired witch hunts or even into timidity-inspired cocoon weaving with red tape, had better read Gellhorn's factual, judicial, and frightening volume on *Security, Loyalty, and Science* (26). Since science and democracy are so akin,² and since this problem transcends science, it behooves scientists to inform the public and their representatives in government of the realities of the situation; for, "its resolution is up to the good sense and democratic wisdom of the American people" (21). It were also well for scientists, through their organizations, to assist socially-minded colleagues who, innocently, have become entangled in security problems—for the welfare of the country even more than of the individuals.

Less terrifying than the danger of outright assassination of intelligence, but more insidious, is that of intellectual starvation. What will happen to originality, to the scientific wild-catter after buried oil for the lamps of wisdom, if projects are organized, teams directed, and funds controlled by great agencies? And this means, of course, government agencies, for:

² "In principle, science and democracy are kin. Democracy, like science, depends on free exploration and discussion. In a genuine democracy the scientific habit of thought is absolutely essential. Decisions are reached after full consideration, from all representative viewpoints, of whatever facts are available and appear relevant; and, since action on any decision soon yields new facts, it can continuously be redirected toward the goal set" (27).

Today the universities are impoverished compared to a quarter century ago. They are really insolvent and carry on only with the aid of funds from industry and especially from government. State and federal funds have supported science in this country for the past decade. If government aid were suddenly withdrawn, I have little doubt that our major educational institutions would collapse. The plain fact is, then, that at present and for the foreseeable future basic science must look to government for support, abetted to some degree by industry; and ever more to the Federal Government (21).

What happens will depend, as in other institutions, on the men in administrative authority. That the results of government support of research can be the very opposite of what one fears, and finds so often as not to require exemplification, can be documented by many bright instances. The Office of Naval Research, responsible for 40 per cent of basic research support in the country today, is not only government, but is military as well. Yet,

Many scientists, like myself, made proposals for ONR contracts a couple of years back, with our fingers crossed. We were a bit tired of the petty bookkeeping problems, the interminable reports, the classified handling of information, the pressure for particular studies, the need for practical orientation that we had all experienced during the war years. But we did make proposals and many received contracts. Since then we have worked with the ONR officers as contractors and a few of us as advisors as well. I can report without reservation not only my own experience but that of all others with whom I have spoken. . . . There has been an irreducible minimum of red tape and paper work, less than for the usual foundation grant; there has been friendly aid always available; there has been no secrecy and no inquisition; investigators have been allowed complete freedom in the prosecution of their research, and immediate or dramatically useful results have not been expected (21).

The Advisory Committee in Physiology, composed of independent civilian scientists, has recommended projects on the basis of scientific importance; and every recommendation has been followed. At one session, the proposal given highest rating was recognized as an extreme long shot, both in objective sought and institution concerned. Yet the investigator was judged competent and sincere and deserving his chance. The National Institutes of Health, United States Public Health Service, have a comparable record of wise policy and decent procedure, as do some other national and state agencies. It is surely a reasonable expectation that the new National Science Foundation will perform as well.

Turning briefly to the positive side of the relation between society, mainly *via* government, and science, there is little question about the situation. In 1947, according to the Steelman Report (28), of one billion dollars spent in support of science, 40 million dollars for basic research, 50 per cent came from Washington. Public Health Service Fellowships today constitute approximately 25 per cent of those available to graduates and post graduates in science in the United States (29). Government laboratories employ close to one-fourth of all the scientists (with Bachelor of Science or higher degrees) in the country and are likely to use a higher fraction as their needs increase

and working conditions continue to improve. Government support of research and training at the universities and related institutions is increasing, as its support for libraries and publication is widespread and widely needed. Again, an increasing contribution by government is essential to develop and exploit the new techniques of communication and inductive discovery. (The great electronic calculators, the operations analysis teams, the Chemical-Biological Coordination Center are government supported.) Travel of scientists and their international congresses are often under government auspices and support; there is general gratitude for Fulbright awards, for subsidies to meetings—as the 18th International Physiological Congress—from United Nations Educational, Scientific and Cultural Organization (UNESCO) and World Health Organization and the like. (Although hosts sometimes remember the three stages in the career of a successful scientist: first he works hard and establishes a reputation, next someone builds him a laboratory, then he shows visitors through the building.)

How, without its own large organizations, could science, in turn, serve the needs of the community and its own devotees? On the international level, far too little is yet possible; although a few cultural (30) and educational (31) missions in the science area have had an amazing influence for good will to and understanding of the United States by the visited nations. One may hope that Fulbright Fellowships will help restore some of that great surge of trust and affection that resulted from the Boxer Fellowships half a century ago. The creation of a science office in our Department of State, closely along the lines recommended by a National Research Council study (32), is a happy omen for the future. One may also hope for increasing support to and vitality in UNESCO, still struggling to remake men's minds the world over on seven million dollars a year. The International Council of Scientific Unions is being strengthened and the establishment of an International Union of Physiological Sciences was enthusiastically approved at the Copenhagen Congress.

But at the national level our organizations are already serving with considerable effectiveness. The National Research Council (NRC), through its office of Scientific Personnel, played a dominant role in bringing about the present wise use of scientists and scholars in meeting the needs of war and peace—the continued education of superior students and hoped-for National Scientific Manpower Board to control the effective allocation of trained men. Last time around the story was very different; despite the vociferous but disorganized warnings of the scientists, this invaluable national resource was squandered unconscionably. The NRC, working with and through the American Institute of Biological Sciences and the Federation in the biological area, has built and administered a roster of scientists that should have great value, whatever happens. In general, the NRC is developing into an open channel between American science and government. The American Association for the Advancement of Science should similarly tie our science to the civilian aspects of the country with a great two-way flow relating science to industry and labor as well as the general public.

Biology has much to contribute towards popular education, civil institutions, national safety, and welfare. Selfishly, also, such contributions are not in vain cast upon the water. Physiologists can take real pride in their great American Physiological Society, which has so regularly taken the lead in good works. It gave powerful support to building up the Federation, to creating the International Union, to vitalizing the Institute, to strengthening the Research Council. It has surveyed the American scene in physiology, encouraged teaching, fostered publications. It has, with many other professional societies promoted research; but it has also, and more than most others, recognized that, in a world growing more complex and organized, science cannot live for itself alone and it has acted with wisdom on this knowledge.

Thus we return to Bacon, whose "Salomon's House," no longer quite so visionary, was envisioned "that human life be endowed with new discoveries and powers." There were ugly undertones in his rhapsody, also not so visionary today:

And this we do also: we have consultations, which of the inventions and experiments which we have discovered shall be published, and which not: and take all an oath of secrecy, for the concealing of those which we think fit to keep secret: though some of those we do reveal sometimes to the state, and some not (1, p. 270).

Science is inextricably bound to government, to industry, to the people, in war and peace, for woe or weal. Science will evermore influence the shape of things to come. Scientists must recognize their social responsibility and must accept their social obligations. In the Western World, it is still possible to function on the basis of co-operation rather than compulsion; scientists must strive to keep it so. Science will become more organized, but must not become regimented. Science, its rational and experimental approach, will in time supply answers to problems beyond its present grasp; it "has already given man a 'utopia of means'; it can yet give him a 'utopia of ends' " (33).

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PHYSICAL PROPERTIES OF PROTOPLASM

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This review covers the period from approximately July, 1949 to July, 1951. Space limitations have prompted arbitrary deletion of subjects such as bacteria, plant structures, technical advances (all of which contain much of interest), and developments in contiguous physical-chemical fields. An understanding of the basic relationships between structure and activity or function makes a separation of physical and chemical properties ultimately quite undesirable. With the one exception of muscle, however, direct connections have been few; although for example, clearly in the offing is the necessity for clarifying those properties of mitochondria which are due purely to structural organization. Breadth of field and space limit not only completeness but also analyses which require a more detailed consideration of work done prior to the period under consideration.

INTRACELLULAR STRUCTURES

Plasma membrane (cell surface).—Free cellular surfaces across which vital molecular traffic takes place (intestine, kidney) possess filamentous projections which, in fixed material, have radii between 0.03 and 0.08 μ and lengths of 0.62 to 1.2 μ [Granger & Baker (1); Pease & Baker (2); Dalton (3)]. For mechanical reasons, such projections might not increase the effective absorbing area by a factor of 30 [see (1)] but may establish selective permeability by necessitating a penetration in depth, a second well-known alternative. The enzymatic role of the cell surface is demonstrated further by the inhibiting effects of uranium on surface phosphatases of yeast [Rothstein *et al.* (4)] and by the experiments of Lindberg (5) using sea urchin eggs in which orthophosphate is thought to be transformed into adenosinetriphosphate (ATP) in a surface layer 0.02 to 0.05 μ thick. In *Tetrahymena* [Seaman & Houlihan (6)], *trans*-12-cyclopentane dicarboxylic acid induces the usually impermeable membrane to pass succinate, acetate, and pyruvate. An increase in metabolism, which is absent in whole cell homogenates, follows. Osterhout (7) has shown that with *Nitella* toxic substances can cause a loss of solute at one point on the cell surface with an entrance of water and consequent death at a remote point. The molecular particle size to which a cell or nuclear surface is permeable is again questioned by the localization of foreign proteins (or products) in the nuclei of reticuloendothelial cells [Coons *et al.* (8)], and in the mitochondria of liver fractions (45). The interaction of cell surface and substrate in determining cell morphology [Weiss &

¹ It is a pleasure to acknowledge the assistance given by Miss Mary Jane Patch of the Department of Biology, particularly in the compilation of Table I.

TABLE I(A)

CENTRIFUGATES OF LIVER FRACTIONS

Method	Ref.	Homogenization	Medium			
				A		B
				Cell Debris Nuclei	Mitochondria	
					Centrifugation	Properties
I. Salt Solutions						
a.	(22)	Grinding in mortar	0.9% NaCl	5 min., 2500 rpm inter. cent.	15 min., 25,000G	Moderate hemolysis (fetus)
b.	(23) (24)	Tissue press with 1 mm. mesh	Alkalinized saline	4 min., 1400G	5 min., 23,000G or 30 min., 2000G	Rich in Phospholipids; poor in nucleic acid (23)
c.	(25)	Grinding a Potter-Elvehjem homogenizer	0.85% NaCl	4 min., 1400G	5 min., 23,000G or 30 min., 2000G	RNA
d.	(26)	Minced in hand-mill, then ground gently in mortar	Isotonic phosphate buffer of pH 7.0	6.5 min., 800G	2 cycles of 25 min., 800G	
e.	(27) (28)		0.9% KCl	15 min., 200G	30 min., 4500G	Cyclophorase system, oxidative phosphorylation
f.	(29)	Tissue press, ground in mortar a Potter-Elvehjem homogenizer	0.85% NaCl with 4 cc. 0.1 N NaOH per liter	4 min., 1400G	5 min., 23,000G	Some esterase activity
II. Sugar Solutions						
a.	(31)	Forced through 20-gauge hypo needle (31)	0.88M sucrose	10 min., 1600G	2 cycles of 10 min., 29,000G	Isocitric dehydrogenase, TPN cytochrome —C reductase (31)
b.	(30) (31)	Forced through 20-gauge hypo needle (31)	0.25M sucrose	10 min., 700G	2 cycles of 10 min., 5000G	Cytochrome reductase a oxidase, octanoic acid oxidase, succinoxidase, isocitric dehydrogenase, TPN cytochrome C reductase (31)
c.	(32)	1 mm. mesh	0.88M sucrose	3 cycles of 10 min., 600G	20 min., 24,000G	Antigen-antibody activity
d.	(33)	Chilled and cleaned	0.88M sucrose	4 cycles of 10 min., 600G	25 min., 20,000G	RNA
e.	(34)	Put through a 1 mm. mesh	1.46M (50%) sucrose, diluted with 0.88M sucrose	3 cycles of 10 min., 1200G	30 min., 18,000G	Acid phosphatase
f.	(35)	Potter tissue grinder	0.88M sucrose 0.14M NaCl phosphate buffer of pH 7.2 (0.01M)	45 min., 500G	15 min., 20,000G	RNA

TABLE 1(B)
 CENTRIFUGATES OF LIVER FRACTIONS (CONT.)

Method		Centrifugation Fractions					
I. Salt Solutions	C		D		E		
	Microsomes		Super-small Granules		Supernatant		
	Centrifugation	Properties	Centrifugation	Properties	Centrifugation	Properties	
a.	60 min., 100,000G	Moderate hemolysis (fetus)			After 60 min. at 100,00G	Hemolysis	
b.	90 min., 23,000G	Rich in nu- cleic acid relatively large amounts of phospho- lipids, (23) RNA (24)	60 min., 95,000G	(23) Poor in lipids rich in nu- cleic acids	After 2 hr. at 95,000G	RNA	
c.		RNA (most)	60 min., 95,000G	RNA	After 2 hr. at 95,000G	RNA (least)	
d.	(1) 15 min. 40,000G (2) 5-6 hr. 60,000G	Anticoagu- lant activity	5-6 hr., 60,000G		After 5-6 hr. at 60,000G	Anticoagu- lant activity	
e.	60-90 min., 25,000G	Succin- oxidase			After 60-90 min. at 25,000G		
f.	90 min., 23,000G	Esterase			After 90 min. at 23,000G	Some esterase activity	
II. Sugar Solutions a.	60 min., 130,000G	TPN cyto- chrome-C reductase (31)			After 60 min. at 130,000G	Isocitric de- hydrogenase	
b.	60 min., 57,000G	Cytochrome- C reductase (635)			After 60 min. at 57,000G	Isocitric de- hydrogenase	
c.	2 hr., 41,000G				After 2 hr. at 20,000G		
d.	4 hr., 20,000G	RNA			After 4 hr. at 20,000G		
e.	150 min. 41,000G	Acid phos- phatase			After 150 min. at 41,000G		
f.	4 hr., 20,000G	RNA			After 4 hr. at 20,000G	RNA	

Garber (9)] is an experimental step in elucidating Weiss' theories of morphodynamics (10).

Erythrocyte envelopes remaining after drying and rehydration [Bessis (11)] and after saponin hemolysis [Schmidt-Thomé & Prediger (12)] have been examined with the electron microscope. They are thin, with evidence of some rigidity. Mitchison (13) reports an envelope thickness of 5000 Å (55 per cent of cell volume), the details of which are forthcoming. A large, fairly asymmetric lipoprotein, showing considerable heterogeneity, has been isolated from erythrocytes [Dandliker *et al.* (14)]. Its content of Rh factor and A and B substances indicate that it may be an envelope constituent.

French & Ada (15) present evidence that an *in vivo* repair of the erythrocyte envelope may take place after receptor destroying enzymes have affected loci responsible for virus adsorption.

Tannic acid treatment [Boyden (16)] will allow erythrocyte surfaces to adsorb otherwise poorly adsorbed protein (serum albumin). Trypsin treatment [Wheeler *et al.* (17); Hubinont (18)] increases the ability of the erythrocyte to adsorb specifically anti-Rh sera, which has been interpreted in terms of the release of otherwise hidden antigenic groups. Trypsin presumably acting on surface proteins has a limited effect [Ponder (19)], increases volume and mechanical and osmotic fragility of human red cells, and produces an unusually rigid ghost. Although the mobility at pH 7.2 is 30 per cent below normal, the erythrocyte isoelectric point is near normal. Little change in disc-sphere or hemolysis properties or heat fragility is observed. The effects of heat in producing fragmentation and hemolysis are detailed by Ponder (20). Saponin and digitonin hemolyze by complexing with the envelope cholesterol (12) and are reported to produce a rigid ghost as evidenced by electron microscopic examination. [For cell hemolysins and anti-hemolysins, see also Table I and Ref. (15).]

Cytoplasm.—The pioneering work of Bensley, the availability of ultracentrifuges, and the striking metabolic properties of mitochondria have emphasized particulates to the extent that cytoplasm is currently treated as a spectrum of particulates in an as yet unknown suspensions medium. A kaleidoscope of patterns emerges from combinations of homogenization, suspension medium, centrifugation pattern, the physical transformations of the particles themselves, their adsorption, differential dissolution, and swelling or shrinking. Schneider & Hogeboom (21) have recently reviewed isolation procedures. Table I (for liver fractionations) compares particles placed by name in the same group, outlines preparative procedures, and lists associated properties. Almost all preparations were made at 0 to 5°C. Equivalent particles should take about 40 times as long to centrifuge in 30 per cent sucrose as in saline, the two commonly used media. Since such a factor is not apparent, the physical properties of the particles in the two media must be different. In a single medium (saline), ephemeral mitochondria are centrifuged in times varying from 5 to 30 min. Timely observations have already been interjected into the traffic of this rapidly developing field. For example, Chambers (36) cautions against the acceptance of fragmentation artifacts. Kopac (37), suggesting that microinjection be used to test media, has found sucrose to be injurious and Kassel's medium to be satisfactory but improved by the addition of ribose or desoxyribose nucleates. That considerably more must be known before general enzymatic activity may be used as an indication of normality is indicated by Seligman *et al.* (38) who find, in agreement with many histological techniques, that treatment with 10 per cent formaldehyde for 24 hr. does not markedly affect certain enzyme systems. In addition to data given in Table I, lipid composition of mitochondria, little different from that of whole liver, is detailed by Swanson & Artom (39). Jeener &

Szafarz (40) report that the smallest granules have the most ribonucleic acid (RNA), but that an even distribution is found in dividing cells. They point out that the former result argues in favor of the normality of the isolated components. In agreement with these results, Barnum & Huseby (24) add that all inorganic phosphorus cannot act as a precursor for RNA phosphorus. Normal liver protein components produced by homogenization having sedimentation constants of $S=3.8, 5.1, 7.5$, and 10 to 11, the latter two polydisperse, are reported by Hogeboom & Schneider (41), who also list proteins from hepatoma where the $S=5.1$ component is absent.

Electron microscopic examination [Mühlethaler *et al.* (42); Dalton *et al.* (43)] suggests the presence of a mitochondrial membrane as does the disintegration of mitochondria by ultrasonic vibrations [see (41)] and the behavior of mitochondrial nonspecific acid phosphatase [de Duve *et al.* (44)]. Harman (28) disagrees and feels that the behavior of mitochondria in salt solutions and water does not require a semipermeable membrane. Crampton & Haurowitz (45) inject radio-iodinated serum and egg albumen and find 30 to 70 per cent of the total activity in the liver mitochondria. They conclude that antibody manufacture is a mitochondrial property. If surface adsorption is not involved, the mitochondrial "membrane" is permeable to large molecules, as is also the case for the plasma membrane. Zollinger (46) has possibly localized small amounts of desoxyribonucleic acid (DNA) in the "membrane." Certain of the serological properties of mitochondria [Malmgren & Bennison (32)] are explained most readily on the basis of the intact structure of the particulate. Addition of citrate and vitrification [Loomis (47)] has been found to stabilize mitochondria. Adenosinetriphosphatase activity appears when mitochondria are incubated in the absence of oxidizable substrate [Kielley & Kielley (48)]; thus, latent enzymatic activities are present, the over-all properties being a function of enzymatic history. [For the biochemical properties of mitochondria, see Bourne (49), Harman (27), Lehninger (50), Judah & Williams-Ashman (51), and Potter *et al.* (52).]

Nyman & Chargaff (53) report that the yeast fraction isolated between 5,000 g for 20 min. and 31,000 g for 105 min. contains lipoprotein particles which contain 22 to 26 per cent lipid and are rich in ergosterol. Almost one-third of the phosphorus in these particles was derived from RNA. Lehmann (54), after electron microscopic observation of the particles of *Tubifex* and the micromeres of *Paracentrotus*, suggests that cell structures are built out of submicroscopic particles of 20 to 500 $\mu\mu$. There is present in tobacco leaves a nuclear protein which resembles plant virus [Pirie (55)]. That virus can be synthesized at the expense of a normal nucleoprotein found in the cytoplasm of the leaf cell is shown by Wildman *et al.* (56).

On fragmentation of retinal rod outer limbs [Sjostrand (57)], discs 60 to 90 Å thick and having the rod diameter are seen with the electron microscope. The central portion of the disc is approximately 30 Å thick with randomly spread dense spots of greater thickness.

Fixation of cell components led Palade & Claude (58) to suggest that the Golgi bodies are fixation artifacts. Gatenby (59) believes that the Golgi net in nerve cells in the living state consists of a cannicular system which can be seen quite clearly. In a similar vein, Xeros (60) and Wallgren (61) report Golgi bodies as 0.5 to 3.0 μ droplets in the pancreas and as a vesiculated system in living plasma cells. Bensley (62) has come to the conclusion that the living Golgi apparatus may consist of vessels or canals containing a watery solution. Bourne (49) believes the Golgi material to be lipid droplets in a state of flux which act as a protective mechanism in the cell. The reviewer feels that the redistribution of Golgi material in the fragmentation-fractionation techniques described above is clearly a matter of concern.

Nucleocytoplasmic interrelationships.—Chambers & Chambers (63) have shown that although fertilized at any time during maturation, the activities of the *Asterias* egg and those of the sperm are synchronized: the development of polar bodies in an immature egg is hastened while the formation of the sperm asters is suppressed. Lorch & Danielli (64) have shown that in heterotransfers of nuclei between *Amoeba discoides* and *Amoeba proteus* (60 per cent successful) the average nuclear diameter and the movement pattern of the individual are a joint product of the nuclear and cytoplasmic origins. The uptake of radioactive phosphorus in enucleated halves of *Amoeba* [Mazia & Hirshfield (65, 66)] is one-third of that in nucleate halves and the decreasing ultraviolet damage series is enucleate half, nucleate half, and whole amoebae. In a similar way, Briggs *et al.* (67) have shown that ova of *Rana*, inseminated with well-irradiated sperm, will produce partial blastulae, but will not develop further even though grafted. By injecting radiated cytoplasm, radiation damage may be transmitted between cytoplasm and nucleus [Duryee (68)].

Nuclei.—Fixed nuclear membranes of *Triturus* or *Xenopus* [Callan & Tomlin (69)] consist of an outer (protein-lipid?) membrane about 300 Å thick having pores 300 Å in diameter interspersed at interpore distances of 800 Å. Supporting the porous membrane is a continuous inner membrane (protein?) about 150 Å thick. Marshak (70) has reported the centrifugation of morphologically and chemically different nuclei. The DNA content of single nuclei for a large number of tissues has been reviewed by Davidson & Leslie (71). An alkali-soluble acidic protein similar to that of Meyer & Gulick and Stedman & Stedman has been isolated from rat-liver nuclei by Wang *et al.* (72). The protein as yet cannot be assigned to the chromosomes. By measuring loss of DNA during maturation, Korson (73) concludes that the nucleus disappears by intracellular dissolution rather than extrusion during erythropoiesis.

Nuclear viscosity has been studied [Harding (74)] by observing the rate of fall of the nucleolus through the nucleus in the starfish egg. From 0 to 35°C., above which temperature gelation occurs, the Q_{10} is 2.7. Below 25°C., thixotropy is evident, for the viscosity decreases with a repetition of the process of measurement.

Rabinovitch (75), using the acid phosphatase reaction, reports semi-lunar blocks of nucleolus-associated chromatin in brain and a continuous ring in liver nucleoli. Nucleoli are the most radiation sensitive cellular elements (68), spindles the least.

Chromosomes.—In the resting nucleus, the absorption of ultraviolet light is diffuse [Ris & Mirsky (76)]. On injury, chromosomes condense, as is also the case where electrolytes are added to chromosomes stained with methyl green and teased out in nonelectrolytes. Chromosomes from which DNA and histone have been removed do not show condensation.

Salivary gland chromosomes [Palay & Claude (77)] are observed with the electron microscope to be composed of transverse rows of small, equally-sized granules, between which, on stretching, a linear network of filaments appears. This network will not appear after preliminary treatment with desoxyribonuclease. Schultz *et al.* (78) have made smear preparations of *Drosophila* chromosomes. Generally in consensus with the earlier findings of Pease & Baker (2), they do not agree that the band character is determined by the structure of the particulate bodies of which it is composed.

Chromosome fragmentation and clumping [Duryee (68)] and an increased fluidity and stickiness [Rugh (79)] are caused by x-rays with no evidence that chromosomes will return to a nondiscrete stage (79). Fragmentation and uncoiling [Newcomer & Wallace (80)] are produced by ultrasonic vibrations. Fragmentation is also caused by treatment with purines and purine nucleosides [Bieseke *et al.* (81)]; an alteration in the metabolism of such compounds is felt to be a possible cause of mitotic aberrations. As pointed out by Denués (82), residual chromosomes (fibrous nuclear fragments) may be used to study chromosomal material where the normal chromosomes are unusually small.

CELL TYPES

Spermatozoa.—The electron microscope has been used [Randall & Friedlaender (83)] to make an extensive examination of ram spermatozoa. Several new structural aspects are described.

Nerve.—Rozsa *et al.* (84) report a vacuolated myelin sheath and a coarse fibrous network within the axis cylinder of fixed rabbit nerve. However, Sjostrand (85) indicates that fragmented osmic acid fixed myelin sheath gives rise to sheet-like fragments having surface regions of high density which resemble retinal rods (see *Cytoplasm*). Unfixed nerve axoplasm from *Loligo* and *Myxicola*, according to Schmitt (86), exhibits filaments 100 to 150 Å wide, which become nodose when treated with formalin. In fixed nerves, nodose filaments 75 to 200 Å wide are observed [Schmitt & Geren (87)]. Since the neurotubules described earlier are actually derived from connective tissue (87), associated virus migration [de Robertis & Schmitt (88)] must be reexamined. In an extensive investigation, Fernández-Morán (89) also finds the myelin sheath to be made up of lamellae 50 Å thick, these being piled on top of each other to form the sheath. The lamellae are covered with

surface granules 50 to 100 Å in diameter as indicated by shadowing. An internal layer of nodose fibrils 100 to 200 Å wide intermediates between the axis cylinder and myelin sheath. Hartmann (90) observes, in formalin-fixed myelin sheath, concentrically arranged placodes 120 Å thick with less dense placodes 61 Å thick in between. Widths and lengths of approximately 800 Å and 1300 Å are assigned. Schmitt (91) has recently reviewed the colloidal organization of nerve.

Electrode polarization causes an increased opacity and shrinkage at the anode with opposite effects at the cathode [Tobias (92)]. Such effects are reversible. Higher voltages and longer times are required with nonpolarizable electrodes than with polarizable electrodes. Calcium or magnesium chloride can reverse cathode, effects and potassium chloride can prevent anodal effects. The author suggests that such effects may be involved in normal conduction. The blocking of nerve excitability [del Castillo-Nicolau & Hufschmidt (93)] by cadmium, calcium, mercury, silver, and potassium (zinc does not block), and its return by thiols, is interpreted in terms of surface groups [see *Plasma membrane, (cell surface)*].

EXTRACELLULAR STRUCTURES

Connective tissue.—Bahr (94) has found that rat-tail tendon may be dissolved in dilute acetic acid, filtered through a fine glass filter, neutralized to pH's between 3.8 and 7, and in this manner reconstituted to fibrils having the usual transverse spacings of approximately 640 Å, the latter being in register. The soluble "procollagen" of Orekhovich, prepared from fresh ground hide by extraction with citrate buffer at pH 4.0, after removal of albumins and globulins, has been characterized. Bresler *et al.* (95) find that it has a partial specific volume of 0.72, a diffusion constant (D) of 2.24×10^{-7} sq. cm. per sec., and a sedimentation constant of $S = 1.8$; from these are calculated a molecular weight of 70000 ± 3500 , a diameter of 16.7 Å, and a length of 380 Å. Linear and lateral dimers form under the action of salt. Bychkov (96) reports that rat-skin "procollagen" will combine stoichiometrically at a pH of 4.1 with hyaluronic and chondroitinsulfuric acids to yield thread-like precipitates. Highberger *et al.* (97), using the electron microscope, find that dialyzed extracts of "procollagen" become fibrous again, showing normal and highly attenuated axial periods averaging up to 2000 Å.

Crystallinity of wet kangaroo-tail tendon is completely lost in 30 min. by 1.2 μ a and 0.3 M.e.v. electron irradiation [Perron & Wright (98)]. Irradiated dry, about 50 per cent crystallinity remains, but samples now show a progressive solubility in water. These soluble materials have not been characterized further. Salo (99) has studied the heat degradation of collagen into a parent gelatin and finds a heat of activation of 20 to 30 kcal. per mole for this formation. Subsequent degradation was found to have a heat of activation of 10 kcal. per mole. X-ray diffraction analysis has led Bolduan & Bear (100) to view the wet collagen fibril as a bundle of filaments in perfect transverse register, thus allowing the bundle to diffract as a smooth cylinder. Register is lost on drying, and the dry fibril now diffracts as a bundle of

smaller filaments. Characteristic small-angle and more variable wide-angle x-ray diffraction patterns [Marks *et al.* (101)] indicate that protein fibers found in skeletal fibers of *Porifera*, axial stock fibers of *Coelenterates*, and body wall fibers of *Echinoderms* belong to the collagen group. Wolpers (102) reviews the normal electron microscope structures of collagen and compares with them the reversible changes which are produced by acid swelling, the irreversible distortion in fine structure produced by *Mixoma* virus, the irreversible changes produced by heat, and the normal appearance of fibers occurring in fibrinoid degeneration. Meyer & Rapport (103) review the five mucopolysaccharides which have been found to constitute the ground substance of connective tissue. Heparin is listed as a possible sixth substance. Dempsey & Haines (104) report, as Day had previously reported, that there may be no mucoid substances in the ground substance of interstitial connective tissue, and they feel that it may be a protein.

Elastic tissue treated with Armour's trypsin [Gross (105)] was found to contain coiled filaments sufficiently numerous to suggest that they represented the formed fibrous structure of this material. Franchi & de Robertis (106) showed such threads to be trypsin solution components, possibly originating from bacteria flagella (107). Gross (177) has obtained evidence which suggests that the coils are possibly an aggregation reaction on the part of components of solutions of trypsinogen. Coiled filaments similar to those of Gross have been seen by the reviewer in fibrous insulin preparations (178).

General.—Chemical treatment followed by staining suggests that the achrosome contains a polysaccharide with a 1,2-glycol grouping which is neither starch, glycogen, nor hyaluronic acid [Leuchtenberger & Schrader (108)]. The pellicle of *Paramecium* [Pigoñ (109)] is shown by electron micrography to be a thin delicate membrane before trichocyst extrusion and a mat-like arrangement of thickened ridges afterwards. The peritrophic membrane in *Dixippus morosus* [Huber & Haasser (110)] is shown to consist of a fibrous network, the holes in the network being covered by a thin film.

The precipitation or coagulation of the jelly coat of sea urchin eggs by extracts from frozen and thawed cells, by cytolyzing the egg, and by nucleoprotein are described by Hultin (111) and Runnström & Monroy (112); the latter have shown that the coagulation effect may be inhibited by 0.5 per cent heparin. They suggest that the coagulum is of a fibrous character. Of interest is the observation of Pease & Baker (2) that the endothelium of glomerular capillaries may not be continuous. The basement membranes of the capillary, about $0.1\ \mu$ thick and ribbed presumably to withstand pressure, may be involved in ultrafiltration. Dalton (3), however, claims that the endothelium is continuous.

PHYSICAL MANIFESTATIONS

Globule-fibril and sol-gel transformations.—That reversible biological sol-gel changes have as their basis a globule-fibril (G-F) transformation is now an accepted view. Muscle proteins show complicated changes which are

sensitive to pH and ionic strength and therefore involve labile bonds. The physical properties of a number of proteins extractable from muscle have been summarized [Weber (113)]. Szent-Györgyi has recently considered the over-all problem of muscle (114). Physical constants of monodisperse myosin are generally: $D = 0.84 \times 10^{-7}$ sq. cm. per sec., and $S = 6.7$ to 7.1 ; consistent with particle weight = 850000 and an ellipsoid 2200 to 2400 Å long, 22 to 24 Å in diameter [Portzehl (115); Mommaerts & Parrish (116)]. Actin, usually polydisperse, is said by Snellman (117) to have a particle weight of 150000. ATP must be present throughout treatments of actin in order to retain reversible G-F transformations [Straub & Feuer (118); Laki *et al.* (119); Mommaerts (120); A. G. Szent-Györgyi (121)]. Straub & Feuer find that the G→F transformation is accompanied by an ATP→ADP (adenosinediphosphate) shift and infer resynthesis of ATP with the F→G transformation. Calcium ion and sulfhydryl groups are implicated. Only the dephosphorylation of ATP during polymerization is confirmed by A. G. Szent-Györgyi (121); neither is found, however, by Dubuisson & Mathieu (122). ATP [A. G. Szent-Györgyi & Joseph (123)] will also make reversible the equilibria established between G- and F-actin by various concentrations of urea and the reversible G-F changes induced by potassium iodide (121). The participation of sulfhydryl groups in actin transformations (as well as actomyosin transformations) is indicated by their inhibition by salyrgan (mersalyl) and reactivation with cysteine [Kuschinsky & Turba (124)]. They attribute the decrease in the viscosity of an actomyosin solution to a dissociation of actomyosin. Dubuisson [(125); see also (122)] finds the electrophoretic velocity of F-actin sufficient greater than G-actin to suggest a difference of 45×10^{-5} acid eq. per gm. using calcium ion as a polymerizing agent, and 3.5×10^{-5} acid eq. per gm. using sodium ion. Depolymerization by sodium iodide is associated with the adsorption of hydrogen ions. Dubuisson (126) finds proteins of contracted muscle extractable with potassium iodide. Determined electrophoretically, they have not been characterized as yet for their ability to show the ATP reactivities of normal actin or myosin.

Kuschinsky & Turba (127) studied the contraction and relaxation of actomyosin with respect to potassium, magnesium, and calcium. They find that contraction is hindered by increasing the calcium concentration to 0.2 M and the pH to 6.9 to 7.3. Under such conditions, ATP leads to a relaxation of an uncontracted actomyosin gel. Again, sulfhydryl and amino groups are implicated. Spicer (128) also finds pH and ionic strength conditions such that addition of actin and ATP immediately to a myosin solution produces a gel. Gelation is inhibited by calcium ion (larger ATP requirement) and enhanced by magnesium ion. Gelation, however, does not appear on adding G-actin to a myosin solution containing ATP. Approximately five times as much ATP is required for precipitation as for gelation. Fabry-Hamoir (129) finds that no pH changes, other than those due to dephosphorylation, occur on bringing actomyosin and ATP together. According to Rubinstein & Grishchenko (130), ATP reversibly lowers hydration capac-

ity of actomyosin to the same extent as is irreversibly produced by heat denaturation. Wollemann *et al.* (131) report a true anisometric contraction via ATP with oriented fibers produced in the presence of 0.005 *M* zinc sulfate. At pressures above 1,000 lb. per sq. in. [Botts *et al.* (132)], a free-weighted actomyosin thread will lengthen irreversibly, the lengthening stopping when the pressure is removed. An inhibition of cross linking is most plausible. Evidence is presented [Botts & Morales (133)] that hydrogen bonding is important in actomyosin interactions.

In the same labile bond category, but sensitive to oxygen tension, are the transformations associated with sickle-cell hemoglobin. Harris & Bunting (134) have demonstrated, under sickling conditions, an increase in viscosity and tactoid formation. Normal and sickle-cell ferrohemoglobin have isoelectric points [Pauling *et al.* (135)] of 6.68 and 6.9 (a difference of about three charges per molecule); they differ also in solubility [Perutz *et al.* (136)] and in sulfhydryl content, normal having two and sickle three moles sulfhydryl per mole hemoglobin [Ingbar & Kass (137)]. Normal hemoglobin (136) forms only isotropic tetragonal crystals, while sickle-cell hemoglobin forms in addition a highly anisotropic orthorhombic needle-like crystal. These differences are not reflected in the x-ray diffraction patterns (136) or the aminoacid compositions [Schroeder *et al.* (138)]. The photographs of Harris & Bunting (134) showing sickle cells are difficult to interpret on the assumption that the membrane of the cell plays an entirely passive role. Pauling *et al.* (135) suggest that sickle-cell hemoglobins react at sites which have a complementary character and which are near the hemes. On oxygenation, the complementary regions are structurally altered and interaction does not take place.

Much stronger bonds are indicated by the properties of fibrils induced in solutions of ovalbumin and serum albumin by heat [Jaggi & Waugh (139)]. These fibrous systems, shown by regeneration to be composed of corpuscular proteins, dissociate only at relatively high pH's. The same is true of insulin fibrils. The high specificity of the growth reaction of insulin fibrils has been shown through its use in an *in vitro* assay method [Waugh, Thompson & Weimer (140)].

It is strongly suspected that many sol-gel reactions are normally enzyme dependent. The series of extracellular reactions involved in blood coagulation [Seegers (141)] and milk coagulation [Berridge (142)] may shed light on this general problem. Sensitive to the action of urea [e.g., Mihalyi (143)], such gels after formation are usually relatively insensitive to ionic strength or pH. Under the simplest circumstances enzyme-catalyzed gelation may have a number of complicating factors. Thus, the quantity of structural fibrin and free fibrin necessary to establish a clot is a function not only of the rate of appearance of activated fibrinogen, but also of the quantities of residual fibrinogen [Waugh & Livingstone (144)]. Sulfhydryl groups have also been implicated in mercaptan-induced protein coagulations [Huggins *et al.* (145)], but these systems have not yet been shown to be reversible.

Protoplasmic streaming.—In myxomycete plasmodia [Kamiya & Abe

(146, 147)], flow amounts to about 4 c.mm. of protoplasm at a cycle, a maximum rate of 1.35 mm. per sec., and is accompanied by a potential difference which usually lags behind physical flow by 30 to 100 sec., or two-fifths to one-seventh of the flow. Loewy (148) has found that, when 5 per cent carbon dioxide is added to the nitrogen gas phase, plasmodia do not disintegrate and streaming will proceed for at least 24 hr. Studies on plasmodia [Seifrizz (149)] indicate that here also anesthesia is accompanied by a protoplasmic gelation.

Sol-gel phenomena have long been implicated in the process of streaming or pseudopod formation. Goldacre & Lorch (150) find that an injection of ATP produces an increased motion of pseudopodia, or in larger amounts, a bubbling over the entire surface of the amoeba, suggestive of the surface aberrations which attend cell division. Heparin produces a liquefaction, a rounding up, and a cessation of movement. Differential production and use of ATP, based on cytoplasmic streaming pathways, is suggested as a possible means by which movement is controlled.

In *Elodea*, constant current [Tobias & Solomon (151)] produces an anodal displacement of chloroplasts and cytoplasm, the vacuole moving to the cathode. Protoplasmic streaming may continue after agglomeration of plastids but will eventually stop. After exposure for 30 min. to 350,000 g [Beams (152)], streaming is inhibited completely. Recovery occurs in this order: Brownian movement and redistribution of cytoplasmic particles, an unorganized streaming, and finally the establishment of organized streaming.

Mitosis.—Considerations of a number of aspects of cell division will be found in the May 31, 1950 issue of the *Annals of the New York Academy of Sciences* (153). Chromosomal fibers, 1500 to 2000 Å in width, possibly banded and made up of subfibrils 200 to 600 Å wide, are found along with fibrous astral rays and interzonal fibers. Continuous fibers are not observed in the crayfish testis [Beams *et al.* (154)] but are observed in the whitefish blastula [Beams *et al.* (155)] and onion root tip [Sedar & Wilson (156)]. Additional evidence that establishment of the division figure requires energy comes from a study of the effects of substituted phenols in phosphorylation by cell free systems [see Clowes *et al.* (157)]; the increased respiration accompanying division [Zeuthen (158)]; the dependence of mitotic activity on oxygen supply, even to the extent of suggesting only aerobic metabolism of glucose [Bullough & Johnson (159)]; and the mitigation of mitotic poisons by glucose [Cornman (160)]. Once established, mitosis proceeds to completion after death [Bullough (161)], in ischemic shock [Bullough & Green (162)], and after separation of plant cells with pectinase [Chayen (163)]. Krahl (164) has recently reviewed the possible relationships between cleavage and metabolism in *Arbacia*. Inhibition of desoxyribonuclease [Marshak & Fager (165)] prevents mitosis. The importance of purine metabolism is also shown by the chromosome abnormalities produced on the addition of purines and purine nucleosides (81). It is interesting to note that thiourea [Rachmilewitz

et al. (166)] greatly increases incidence of mitosis in liver without causing necrobiotic changes.

That the amphiastral figure may be established in the complete absence of chromosomes is evidenced again in the work of Briggs *et al.* (67) in which eggs, fertilized with irradiated sperm and then enucleated, cleave with an asymmetric distribution of chromatin fragments, and that of Ris (167) who has uncoupled spindle and chromosome factors with chloral hydrate.

Radiation studies indicate the times at which the physical-chemical processes underlying spindle development are most sensitive. Thus, eggs undergo a period of sensitivity to ultraviolet light, *Chaetopterus* eggs about 30 to 40 min. [Gross (168)] and *Arbacia* about 10 min. after insemination [Marshak (169)]. They are less sensitive later in the mitotic cycle [see also Blum *et al.* (170)]. As in other systems, subsequent irradiation with visible light can alleviate the irradiation damage of ultraviolet light (169, 170). X-ray damage to amphibian material has indicated the spindle to be most resistant, the nucleoli least resistant, with chromosomes intermediate [Duryee (68)]. Similar changes are reported by Rugh (79).

It has long been known that the mitotic apparatus involves reversible sol-gel or viscosity changes. Wilson (171) finds a post fertilization decrease in rigidity, a return to normal, and a decrease again just before division. Harding (172), using acidic injury substances from *Arbacia* to cause parthenogenesis, describes an increase in protoplasmic viscosity just before division. The effects of a number of agents, such as heparin, bacterial polysaccharide, and vitamin K, which prevent cell division by solation have been detailed by Heilbrunn & Wilson (173). Colchicine [Northen (174)] acts also by causing a decrease in structural viscosity in the onion root tip; an increase in cell volume unaccompanied by cell division follows.

A study of temperature-pressure effects [Marsland (175); see also (176)] has shown the cortical protoplasm to be an endothermic gel involving a volume increase on gelation. It is suggested that energy stored during gelation is used in the process of division, in agreement with the fact that, once initiated, divisions proceed to completion. ATP has also been suggested as a source of energy.

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GROWTH¹

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In this field of investigation, as in the others, our scientific heritage should be kept in mind. With respect to the rate of growth, for example, Minot (1) concluded that it is greatest during the segmentation of the ovum, that it declines so rapidly that at birth about 98 per cent of this power has been used up, and that the remaining 2 per cent is largely exhausted in infancy; "but before senescence conquers, the germ cells are set free, effecting rejuvenation" (2); "death is the inevitable price which the organism must pay for the cytological differentiation on which all later life depends" [(2) Minot's "cytomorphosis"].

The present review is based chiefly upon work published during the period from July, 1950 through June, 1951, but in accordance with the suggestion of the Editor, it takes into account some of those contributions of the preceding year which were not cited in two recent reviews (3, 4). Sexual differentiation and the development of function are emphasized. Many of the references and certain important aspects of growth, notably molecular morphology (5) and neoplastic growth in animals (6) and plants (7), are not given the attention they deserve.

PRENATAL (EMBRYONIC) GROWTH

Several phases of this subject are considered in two new books on embryology (8, 9). Not covered is the fact that, in studying the growth of mammalian embryos, it is well-nigh impossible to segregate the genetic factors from intra-uterine factors. This segregation may be accomplished in part by using embryos which are obtained by transplanting fertilized rabbit eggs into the uteri of does of different breeds (10).

Other recent contributions deal with genes (11, 12, 13), unfertilized eggs (14), segmentation without fertilization (15, 16), fertilization (17, 18), desoxyribonucleic acid (19), segmentation after removal of the chromosomes (20), triploidy (21), haploidy and diploidy (22), enzymes in the utilization of yolk (23), energy for cleavage (24), inhibition of segmentation (25, 26), gastrulation and neurulation (27), young human ova (28), mammalian proamniion (29), and a graded series of chick embryos (30).

Embryonic induction.—When structural manifestations of this early phase of differential growth first become discernible, it may be too late to study the causative factors. Such terms as embryonic competence and developmental field have only limited value (31). They are useful, for ex-

¹ It is a pleasure to acknowledge the assistance of Dr. Margaret W. Cavanaugh in assembling many of the references cited.

ample, in designating certain physicochemical factors in those regional differences which appear in the developing central nervous system (32). It is not clear, however, whether these differences are attributable to gradients of distribution of a single inducing substance (33) or whether the inducing agent is a mosaic of different substances (34, 35). Ribonucleic acid may be one factor in induction (36), but it remains to be determined whether it is the causative factor in, for instance, the selective stimulation of growth of certain nerve fibers by transplanted tumors (37). There are recent studies of gradients and polarity (38, 39, 40), role of physical contact (41), and effects of partial notochordectomy (42).

Differentiation.—Two large contributions in this field are a clear statement of the problem of modulation ("premorphological differentiation") and a recognition of the fact that the inherent complexity of problems of differential growth cannot be circumvented by using such ambitious but loose designations as "chemical organizers," "growth substances," "differentiation hormones," and "embryonizing effects" (31, 43). Differentiation is said to be nonreversible and is preceded by modulation (preliminary changes which do not abolish the state of flux); accordingly, modulation is a more comprehensive term than competence. That this view of nonreversibility is debatable is reflected by the existence of the term "dedifferentiation." Modulated tissue has been studied by means of the precipitin reaction (44). The specific antigens may turn out to be "organ forming substances."

Other published records deal with differentiation in transplanted ova (45, 46), ova subjected to sex hormones (47), transplanted blastocysts (48), cultured blastocysts (49), neuroblasts of the midbrain (50), neurons (51), cerebral cortex (52), cultured brain cells (53), transplanted spinal cord (54), reversed medulla (55), otic vesicles (56, 57), transplanted indifferent tissue (58), propigment cells (59), premyocyte (60, 61), cultured bone (62), and transplanted hepatic (63) and metanephric (64) tissue.

Sexual differentiation.—There is still a lack of agreement as to whether hormones from the embryonic gonads govern the differentiation of the accessory reproductive organs, especially in mammals. Certain workers, notably Burns, maintain that Lillie's well-known explanation of the freemartin is a conception which is useful in trying to arrive at a common denominator for the control of sexual differentiation in the several classes of vertebrates (65, 66). Moore's observations lead him to the opposing view that the proper explanation for the freemartin condition has not yet been suggested (67); he regards as an open question whether secretions from the developing gonads exert any influence upon the critical (early) stages of sexual differentiation in mammals.

Fetuses have been deprived of the gonads by castration (68, 69, 70) or by irradiation (71, 72, 73). Using quantitative data, it has been virtually proven that the testes of fetal rats produce a hormone (androgen) which stimulates the prenatal growth of the genitalia (74, 75); some of the work in fetal rabbits and mice points to the same conclusion (70, 73). Although crys-

talline androgen prevents all the physiological effects of castration (75), an attempt to prevent these effects by grafting testes was largely unsuccessful (76). It is reported that in some cases the genitalia of castrated fetuses are feminized (70, 73). The reviewer believes that it remains to be determined whether the first production of testicular androgen antedates (a) the earliest step in the differentiation of the accessory reproductive organs and (b) the "modulation" of the primordia of these organs.

Fetuses have been deprived of the hypophysis by decapitation (68, 69, 70, 74) or by irradiation (71, 77, 78); but it has not been proven that the fetal hypophysis produces a gonadotrophin. In "hypophysectomized" fetuses, the testicular interstitial cells are reported to be normal (73), slightly abnormal (74), or markedly atrophic (70). The germ cells in the testes and ovaries are fewer than in those of controls (73). The testicular interstitial cells are endocrinologically labile since injected gonadotrophin increases their number, size, and granularity in intact fetuses and in "hypophysectomized" fetuses as well (74). These modified cells show an abundance of osmophilic lipids.

A recent view of sexual differentiation in mammals is (a) that the testicular secretion induces the formation of the "male genitalia" and prevents the appearance of "female genitalia" in males; (b) that the action of the testicular secretion is largely local or unilateral; and (c) that the embryonic ovaries do not influence sexual differentiation (69, 70); this view has a number of shortcomings (79). In fact, several of the abnormalities observed in castrated fetal rabbits may also be produced in rats by feeding the pregnant mother a diet which is deficient in vitamin A. Prostatic tissue does develop in the females of certain mammals. Injected crystalline androgen fails to prevent the formation of derivatives of the Müllerian ducts in females. When the Müllerian ducts are grafted into the eyes of adult hosts, the testicular secretion in the male hosts does not prevent them from developing into uterine tissue (80). The results of unilateral castration and of "sham" castration do not support the conception that in fetuses the action of the testicular secretion is mostly local or unilateral (81). On the other hand, the conception that the ovaries fail to influence differentiation is acceptable despite the report that the destruction of the ovaries of fetal mice by irradiation is followed, in some cases, by a failure of retrogression of the lower portion of the Wolffian ducts (73). In fetal rats, indeed, the injection of chorionic gonadotrophin does not stimulate growth of the ovaries (74). Also, in ovariectomized fetal rabbits, the genitalia resemble those of controls (70).²

Any satisfactory theory of sexual differentiation must reckon with observations which are so numerous that only a few may be mentioned. Certain spontaneous hermaphrodites have ovotestes and some degree of

² Although congenital absence of the ovaries in children is of special interest (82), we do not know that the ovaries had been missing prior to the earliest stage of differentiation of the accessory reproductive organs.

completeness of two sets of genitalia, male and female (74, 83). Under special conditions, the testes of pouch-young opossums may be modified experimentally by injecting estradiol under the skin; the germinal epithelium remains active and forms a cortical zone which simulates that of an ovary (84). In transplantation experiments, though, the sex hormones of adult hosts do not influence the pattern of development of grafted embryonic gonads (85, 86). When mouse ovaries are grafted into ears, the developing medullary cords seem to arise as ingrowths from the germinal epithelium (87). The external genitalia of the freemartin are essentially like those of a normal bovine female (88); those special features of hermaphroditism which are found in the freemartin have not been experimentally duplicated in any mammal. In female monkeys converted into intersexes by introducing androgen into the circulation of the gravid female, the external genitalia are decidedly masculinized (89, 90, 91); after birth by caesarian section, the time of attained menarche is normal (89); the urogenital sinus persists, and, when adulthood is reached, such structures as a veritable prostate and seminal vesicles are found (90).³ The European mole is unusual in that the female shows normally a high grade of persistence of the Wolffian ducts (93).

Similarly, we do not seem to have any theory which will satisfactorily account for all the recent observations in birds. The introduction of estrogen into incubated eggs tends to convert males into intersexes by activating the germinal epithelium of the developing testes (94, 95). A masculinization of the female may be induced, of course, by performing a unilateral ovariectomy after hatching [a subject recently considered by Benoit (96)]. From grafted bits of blastoderm, it is possible to obtain sterile gonads which resemble sterile testes (97), thus suggesting that germ cells are necessary for the formation of an ovary; but the destruction of the germ cells by ultraviolet light may be followed by the development of sterile testes and of sterile ovaries as well (98). It is thought that sexual differentiation in females does not require hormones and that the testes influence differentiation only by producing an "inhibiting hormone" (99, 100). "Castration" by irradiation inhibits the retrogression of the Müllerian ducts in (male) chick embryos (101)⁴ but does not modify the syrinx and genital papilla in duck embryos (102). In female chick embryos, agenesis of the usual Müllerian derivatives may be induced by means of injected androgen, sulfa drugs, or arsenic (103).

A wide range of intersexuality in amphibians (104 to 109) and in fishes (110) may be brought about by means of introduced sex hormones. That the normal differentiation in amphibians is not effected exclusively by these hormones, however, is suggested by the fact that in larval frogs (*Rana*) the action of administered cortisone is antiovarigenic. Cortisone leads to

³ The ease of inducing changes in the embryonic cloaca suggests that its early development involves a series of Weiss' modulations (92).

⁴ The earlier work of Willier & Yuh (384) had shown, however, that lowered temperature alone caused a persistence of the Müllerian ducts in males.

the development of males in 100 per cent of the cases (111).⁵

Such fishes as the eel show a transitory hermaphroditism which persists through the juvenile period (115). In *Anableps*, the formation of the male copulatory organ from an unspecialized fin is attributed to the action of androgen from the developing testes (116).

The development of the gonads is not fully understood. Experiments in urodeles suggest that the genital ridges originate from the peritoneum and that the gut endoderm acts as embryonic organizer (117). An opposing view is that in amphibians and birds the medullary portion of the gonad and the cortex of the adrenal originate in common from a single blastema (118). A study of tagged cells might assist in solving the problem.

Morphogenesis.—In explanted blastoderms, morphogenesis seems to require more carbohydrate than does differentiation (119). Blastoderms subjected to rabbit antisera against embryonic tissues go to pieces (120). The death of certain cells may contribute to morphogenesis in such developmental processes as the union of separated primordia, cavitation of solid primordia, and rupture of the oral and cloacal membranes. Dying or dead cells may be found in almost any region of a normal embryo.⁶ Cellular death is most evident in those regions where the close packing of cells would seem to militate against a free movement of cells (121).

That language difficulties sometimes assert themselves in science is illustrated by the outcome of a restudy of Dohrn's *Torpedo* specimens. Errors in translating one of his words ("*Verbindung*"=connection) must have led to the theory that the hypophysis cerebri is a homologue of the preoral pit in *Amphioxus* and of the proboscis pore in *Balanoglossus* (122).

The recent literature includes reviews of morphogenesis in animals (123) and plants (124). Other investigations deal with slime molds (125), "essential growth factors" *in vitro* (126 to 130), oxygen requirement (131), skin and cutaneous appendages (132), mammary glands (133, 134), pigment in hair (135), spinal cord (136, 137), innervation of teeth (138), endolymphatic sac (139), craniopharyngeal canal and misconception of it [(140, 141) canal in 9 per cent of newborn infants (Arey)], pulmonary alveoli (142, 143), prostate (144), pronephros and mesonephros (145, 146), renal efferent arterioles (147), adrenals and gonads (148), azygos vein (149), fat (150), cartilage and bone (151), new type of chondrification (152), cultured bone (153, 154), stoppage of bone growth *in vitro* by added alizarin (155) and by hypervitaminosis A (156) but not by added hyaluronidase (157), ossification in sheep (158), knee joint (159, 160, 161), hip joint (162), elbow joint (163), and incudomalleal joint [the one which seems to allow movement of the

⁵ A similar outcome of 100 per cent males has been observed in untreated triploid frogs (112) and in toads (*Bufo*) obtained from a special cross [eggs from male intersexes \times sperm from normal males (113)]; in a number of the vertebrates, incidentally, the exact behavior of the sex chromosomes is not clear (114).

⁶ Hartman once challenged the late Dr. George L. Streeter to show him one embryo, any age, that did not have some dying cells in it (383).

fetal jaw prior to the formation of the temporomandibular joint (164)].

Development of function.—In regard to the developing endocrine glands, some of the earlier observations suggesting that the fetal hypophysis produces adrenocorticotrophin (165, 166, 167) have been confirmed (168, 169, 170) and extended (171, 172, 173). Unilateral adrenalectomy leads to a compensatory hypertrophy of the remaining adrenal (171). The adrenals do not produce any appreciable quantity of androgen [not enough to prevent the effects of castration (172)]. Implanted crystalline sex hormones do not influence the growth of the adrenals (174).⁷ While the thyroid of a fetus "hypophysectomized" by decapitation is smaller than that of a control (176, 177), it has not yet been proven that the fetal hypophysis produces thyrotrophin. Injected thyrotrophin accelerates the growth of the thyroid in normal and "hypophysectomized" fetuses (178). Thiouracil fed to pregnant rats causes an hyperplasia of the thyroid of the newborn (179). The thyroid of the chick embryo will take up radioactive iodine as early as the eleventh day of incubation (180). Development of the amphibian thyroid may be inhibited by administered testosterone (181). The islets of Langerhans contain alkaline phosphatase before birth (182), but the significance of this is not clear. In transplanted fetal pancreas, only the ducts persist (183). The functional development of the endocrine glands has been ably reviewed (79).

Turning to the cardiovascular system, the heart of a chick embryo will resume its pulsations after having been frozen in liquid nitrogen and then thawed out (184). The degree of mixing of the two caval streams of blood has been studied in guinea pigs by means of radioactive phosphorus (185).⁸ The lumen of the ductus arteriosus begins to diminish before birth (188), but the duct carries a bit of blood for some time after birth (189). The blood fructose of fetuses seems to originate in the placenta from glucose (190); why do fetuses need fructose? The answer not being apparent, we may proceed by noting that the fetus gets ample iron from the maternal plasma (191). An autohemolytic agent has been found in saline extracts of the fetal liver (192). The uptake of oxygen by embryonic chick blood increases prior to the nineteenth day and then levels off (193). That a great deal of blood enters the fetal lung is suggested by data on the iron content of lungs (194) and by the relative size of the pulmonary vessels (195).

The functional development of the nervous system of guinea pig fetuses reaches a critical stage at about the fortieth to forty-fifth day. At this time the cortical phospholipids increase (196), the nuclei of the cortical cells (neurons) attain their final volume (197), the amount of intracellular water is increased (198), and an electrostimulation of the cortex causes muscular responses (199).⁹ In amphibians, cholinesterase activity is first detectable

⁷ That injected cortisone does not modify the growth of fetuses is suggested by observations in preliminary experiments (175).

⁸ This substance is rapidly taken up by the tissues of chick embryos (186, 187).

⁹ The development of the pattern of fissures in the sheep brain has been attributed to "intrinsic" factors (200).

in the spinal cord at a time when the embryo will first respond to tactile stimuli (201).

Muscular contractility develops in advance of striation (202). Sheep fetuses of 70 days show myogenic and neuromotor activity and have the ability to swallow (203).

Regarding the kidneys and digestive tract, some earlier experimental evidence of the secretion of urine by the fetal kidneys (204) is supported by the report that in human fetuses this secretion is radiologically demonstrable as early as the fourth to fifth month (205). On the other hand, the exploratory work on the fate of food introduced directly into the fetal stomach (206) has not been extended.

Ponderal growth in fetuses.—Of two papers on dog fetuses, one records the variation in the weight of litter-mates (207). In a litter of eight "mongrel" fetuses, the largest one weighed 2.6 times more than the smallest. While this litter may have been sired by more than one male, the observed difference in weight serves to remind us of the many advantages of using in experiments not only litter-mate controls but an inbred strain as well. The second paper presents growth curves of the kidneys and bladder (208).

In the hamster fetus, it has been concluded that "three periods of uniform weight increase occur, each succeeding period being at a higher rate" (209). Presumably the authors made the mistake of not converting a daily increment into the percentage of the weight at the beginning of that day. Working with the data presented, the reviewer's calculations show that, percentage-wise, the increase per day actually dropped from 11.9-fold (day 9 to 10) to 0.57-fold (day 15 to 16).

Evidently another worker has made the same mistake since he has written (210, p. 5),

The uterine tissues that have undergone hypertrophy in the middle of pregnancy are drawn out to accommodate the fetus as it enters its period of most rapid growth.

This does not discredit, of course, his important observations on the growth and contraction of the gravid uterus (210, 211).

Inhibition of development.—This may be induced by such substances as cortisone (212), pteroylglutamic acid antagonist [4-amino-folic acid (213)] and lithium (214, 215). Some effects of lithium have been known for several years.

Developmental anomalies.—Those produced by feeding diets which are deficient in vitamin A (216), riboflavin (217), or pantothenic acid (218) ought to have some common denominator with respect to the causative metabolic disturbance. Perhaps the carbohydrate metabolism is disturbed; pyruvic acid will prevent injected insulin from causing anomalies (219).¹⁰ Other studies deal with fetuses *in fetu* (223), double ureter (224), the effects of ultraviolet light (225), hypophyseal extracts (226), lowered oxygen (227),

¹⁰ It is not clear why neoplastic growths may be produced by irradiating rat embryos (220); the grafting of tissue may also lead to neoplasia (221, 222).

aneuploidy (228), and metrazol (229). Experimental teratogenesis in birds has been reviewed (230).

POSTNATAL (POSTEMBRYONIC) GROWTH

Histochemistry, cytochemistry, and enzymes.—Numerous advances have been assembled in three extensive treatises (231b, 232, 233). The nucleus of the cell is thought to be the main, but not the only, center for the synthesis of proteins (231b) [cf. (231a)]. Derivatives of ribonucleic acid may be involved in the effects of irradiation upon mitosis (234). Human saliva contains a "growth promoting factor" other than vitamin B₁₂ (235). There are papers on carbonic anhydrase (236) and the decline of phosphatase during mineralization (237).

Genetic and morphological aspects.—The chromosomal constitution is not necessarily the same in all somatic cells, a point observed in the larvae of parasitic wasps (238). The genes (239) influence, of course, the regional differences in growth (240). In mitosis, only the earliest stages are thought to require sugar as a source of energy (241). The rate of mitosis may be increased by nonspecific injuries (242) and by adding coramine to the diet of mice (243). The mitotic activity during compensatory hypertrophy of the kidney, following unilateral nephrectomy, reaches a peak within one to three days (244, 245). Other papers on the morphological aspects of growth deal with the cranial vault (246), shedding of antlers (247), teeth (248, 249), inferior alveolar nerve (250), tibia (251), pancreas (252), and lymph nodes (253).

Ponderal growth.—"Normal" body weight, defined actuarially, tends to obscure two features of aging, namely deposition of fat and replacement of some of the muscle by adipose tissue (254). In rats there seems to be an inverse relation between body weight and fecundity (255). In a heavy strain of rats, the metabolic rate is reported to be essentially like that of controls (256). Four papers present the relation between the body weight and weight of organs (257 to 260), and one deals with the ponderal growth of insects during moulting (261).

Growth equations.—All growth equations are empirical. They assist in depicting the pattern of change in size and of change in shape (262).¹¹ In constructing and using them, an important objective is that of disentangling curves of growth from curves of "frequency distribution" in size (264). A new method of estimating differential (allometric) growth gives greater accuracy than the older methods (265). By means of "shape parameters" (ratios, if the growth is isometric) and allometric constants, it is possible to construct a growth profile of an organism (266).

Transplantation, tissue culture, regeneration, wound healing.—During the period reviewed, it would seem that there were not any major advances in these fields (cf. the effects of hormones upon the healing of wounds).

¹¹ See a thoughtful review of the second edition of D'Arcy W. Thompson's book, *On Growth and Form* (263).

Papers on transplantation deal with the outgrowth of nerves (267) and with the growth of transplanted cornea (268), hypophysis (269), thyroid (270, 271), adrenals (272), spleen (270), and gastric mucosa (273). In the vast literature on tissue culture there are articles devoted to cutaneous epithelium (274, 275, 276), cerebral tissue (277), ganglia (278), cardiac tissue (279), and fibroblasts (280, 281). The work on regeneration has been done on structures of various animals: unicellular organisms (282), coelenterates (283) following mechanical dissociation of the cells (284), flatworms (285), roundworms (286), earthworms (287, 288), isopod crustaceans (289), axolotls (290, 291), amphibian eyes (292, 293, 294), nerves (295, 296, 297), mammalian liver (298), and submaxillary gland (299). There are papers on the healing of fractures (300) and of wounds in the skin (301) and vagina (302).

Nutrition, appetite, vitamins.—In regard to nutrition and appetite, the growth of domestic animals (303) and of man (304, 305, 306) may be speeded up or slowed down by modifying the level of nutrition. The protein and amino acid requirements in mammals have been extensively considered (307). Choline, a lipotropic agent (308), is used therapeutically in cirrhosis (309). A recent monograph presents the results of the "Minnesota experiment" on semistarvation (310). It is argued that the increased appetite which follows certain lesions in the hypothalamus consists of two components ("voracious appetite" and "discrimination"), either one of which may be governed in part by the amount of stored fat (311). When an area in the lateral hypothalamus is bilaterally destroyed, however, the urge to eat is abolished (312). In a strain of mice with hereditary obesity (313), the animals ate more fat, less protein, and less carbohydrate than the controls [glycostatic theory (314)]. In the *dba* strain, a high fat diet seems to hasten a bit the aging of the skeleton (315).

An important advance is the observation that the growth of animals may be increased by adding to the experimental diet the "animal protein factor" [made from cultures of microorganisms (316, 317, 318)], or such antibiotics as aureomycin (316, 317, 319 to 323) and streptomycin (318, 321, 324). The "animal protein factor" may contain some essential factor(s) other than vitamin B₁₂ and antibiotics (317). It would seem that the antibiotics act by reducing the number of certain intestinal microorganisms (325, 326, 327). In rats fed a diet in which DL-methionine is the only source of amino acids, the usual reduction in growth and also the abnormal uremia in the newborn may be prevented by added phthalylsulfathiazole (328).

The water-soluble (329) and fat-soluble (330) vitamins have been considered in recent reviews. A monograph on the biochemistry of the B vitamins (331) and a collection of literature on vitamin E (332) have been prepared.

Effects of hormones.—The effects of auxin, the growth hormone in plants (333), and of the hypophyseal growth hormone (334) have been reviewed. One hypophyseal preparation used, a somatotrophin, was not electrophoretically pure (335). Injected hypophyseal growth hormone prevents a loss of

weight (336) and reduction in lymphoid tissue (337) after hypophysectomy, activates the proximal epiphyseal plate of the tibia (338, 339), acts synergistically with thyroxin in causing growth of the long bones (340, 341), and speeds up the synthesis of proteins (342, 343). Its diabetogenic action has been confirmed (344, 345), but its insulinotrophic effect upon the pancreas has been questioned (346). It promotes growth of the islets of Langerhans (347), increases the excretion of glucose in alloxinized rats (348), and causes hypoglycemia during the "postabsorptive state" (349). It accelerates the turnover of liver phospholipids (350) and seems to be a factor in water metabolism (351). It failed to increase the growth of rats subjected to low temperature (352), to influence the regeneration of plucked feathers, (353) and to prevent that reduced ossification of the os penis which follows castration (354).

As to other hormones, injected androgen doubled the rate of growth of female monkeys (355) and increased the rate of maturation of the skeleton and of eruption of the teeth (356, 357). Parathyroid extracts first cause a rapid resorption of bone in rats and then a regeneration of it (358). Cortisone seems to disturb the normal osteolytic activity (359). Adrenocortical steroids slow down the healing of wounds (360) and fractures [(361), except in the guinea pig (362)], as does also ACTH (363).

Inhibition of growth.—We may pass over the specific antibiotic substances by mentioning a recent survey of the subject (364) and a handbook (365). A notable advance in specific inhibition of growth is the observation that injected astaline, a radioactive element produced by "bombarding" bismuth, virtually destroys the thyroid in the rat and monkey without causing appreciable damage to other organs (366, 367). This might be developed, for example, into a method of "thyroidectomizing" fetuses.

Growth may be inhibited by fasting (368) and by the action of β -rays (369), x-rays (370, 371), ultraviolet light (372), ultrasonic energy (373), low temperature (374), extremes of pH (375), certain colloidal (vital) dyes (376), sulfhydryl inhibitors (377), triethylcholine (378), fluorides, and aminopterin (379). Regarding hormones, estrogen inhibits the growth of hair in rats (380). Adrenocorticotrophin (381, 382) and cortisone (382) inhibit the ponderal growth of rats.¹²

ADDENDUM

Certain workers, especially embryologists, will be interested in examining a recent monograph on the neural crest (385).

¹² Injected cortisone is reported to hasten the eruption of teeth and developmental opening of the eyes of baby rats (382).

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THE PHYSIOLOGY OF THE CONNECTIVE TISSUE^{1,2} (LOOSE AREOLAR)

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In an attempt to review the physiology of the connective tissue, the field could perhaps properly be made so all-inclusive as to encompass embryology, histology, physiology, and every scientific discipline of the biological world. However, because of space limitations it is not possible to consider more specialized tissues derived from the mesenchyme, such as skeletal and smooth muscle, bone, cartilage, fat, blood vessels, and the hematopoietic system. The main purpose of this review, therefore, will be to consider the loose connective tissue (or loose areolar tissue) of the adult organism to which four definite functions have been ascribed: (a) support, (b) transport, (c) storage, and (d) repair (healing) and protection (antibody formation). Another possible function which may be ascribed to this tissue is that of regulator of salt and water in the organism (49). In certain instances, major topics will be mentioned briefly only by reference to recent review articles.

The discussion will be directed towards the physical and chemical properties of each of the three major components of the tissue—the amorphous ground substances, the fibrillar elements, and the cells. Since an understanding of the physiological reactions of this tissue requires some knowledge of its development, considerable attention will be paid to this phase of the problem. Structure is apparently important in development, particularly of the fibrous elements, and this will be discussed. At times, structure can be related to function, while often this relationship is not apparent.

Bailey (12), Maximow & Bloom (111), and Ham (80) give a clear picture of the development of connective tissue from stellate cells and syncytium of embryonal mesenchyme. In the development of embryonal to adult tissue, the derivation, from stellate mesenchymal cells, of macrophages (in various terminologies labeled histiocytes, clasmotocytes, pyrrhol cells, adventitial cells, resting wandering cells, endothelial leukocytes), mast cells, fibroblasts, and endothelial cells (which evolve into capillaries and larger vessels) is accepted as established. During embryonal development, ground substance is believed to be derived from embryonal syncytium, which is presumably

¹ The survey of the literature pertaining to this review was concluded in June, 1951.

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secreted by the stellate cells of the mesenchyme (12, 80, 111). Following the embryonal stage, when one discusses connective tissue rather than mesenchyme, unity of opinion no longer exists concerning the origin of the various components of the tissue.

GROUND SUBSTANCE

In the adult, the glycoproteins (or mucopolysaccharide-protein complexes) of ground substance have been the subject of intensive study by histochemical means as well as by isolation techniques. The former have been described by their most earnest advocates as crude and in many instances nonspecific (24, 64, 87, 95, 113, 185, 201). With isolation techniques, exact localization of the tissue extracted is impossible, and during the processes of extraction the material is degraded, denatured, or depolymerized to a certain extent. In adult tissue, ground substance may be secreted by fibroblasts (64, 108) or by mast cells from an heparin-like precursor (7). To the mast cell has also been ascribed the elaboration of heparin (134, 138, 200) which may be associated in this cell with a specific lipoprotein (or heparin cofactor) (174). Alkaline phosphatase found in mast cells may be concerned with the extrusion of the metachromatic substance of mast-cell granules (156), which are rapidly ejected from the cells following the stimulus of a bacterial pyrogen given intravenously (183). Secretion of ground substance is probably mediated by vitamin C since in scurvy very little metachromatic material is present in regenerating connective tissue (141). Mast cells have been said to secrete synovial fluid hyaluronic acid (6), and synovial cells grown in tissue culture have produced a "mucin" (194).

Gersh & Catchpole (64) have carried out extensive histochemical studies on the ground substance, which is a mucopolysaccharide-protein complex (glycoprotein) as stained by the McManus-Hotchkiss techniques. It may vary, they feel, in a reversible manner from a rigid gel to a more or less fluid resistant state, depending chiefly on the rate of replacement of glycoprotein, possibly through secretion by fibroblasts, and on the degree of depolymerization of the glycoprotein caused by enzymes of the mucinase class. The glycoprotein of the ground substance in mice becomes more highly polymerized at about the time of birth. This polymerization is greatest at the site of formation of the basement membrane. The younger material is water soluble and with maturation becomes insoluble and more highly polymerized (28).

Meyer and his co-workers have isolated hyaluronic acid (a high polymer of N-acetylglucosamine and glucuronic acid), which is polydisperse as isolated from nature (122, 124). Three types of chondroitin sulfuric acid (polymers of N-acetylgalactosamine, glucuronic acid, and sulfate), different in specific rotation and in enzymatic reaction, have been isolated from various sources (123, 125 to 127). It has been estimated (140) that in 100 gm. of fresh human skin there are approximately 24.5 mg. of hyaluronic acid and 26.2 mg. of chondroitin sulfuric acid. Hyaluronidase, an enzyme which

hydrolyzes hyaluronic acid and certain chondroitin sulfates, has been studied extensively (122). Histologically (17), in development and aging, as well as in repair, a progressive series of changes have been found to take place in areolar connective tissue with a shift from the amorphous to the fibrous elements of the intercellular substances. Hyaluronidase speeds up this process (17). Evidence has been presented (36, 37), from histological techniques in conjunction with pH changes and dehydration, that the interfibrillar material is membranous in nature and that the collagen bundles are held together by an amorphous cementing substance which is modified by trypsin (34, 35). From these characteristics, Day deduced that, in the ground substance, protein with an isoelectric point about 4.5 is present which, when modified, loses its physical properties (38, 39, 41). An hyaluronidase-sensitive mucopolysaccharide, by its macromolecular properties, may act as a "waterproofing" of the connective tissue (40) which in essence is a fabric of protein fibers. Isolated sodium hyaluronate has been examined with the electron microscope and found to be without definite structure (74). It has been generally agreed that, in loose connective tissue, the ground substance is a mucoid (122) with a rather firm linkage between protein and acid mucopolysaccharide—perhaps a chondroitin sulfuric acid.

Dyes pass through the connective tissue in thin films probably held to the fibers by surface forces (115). In the hematoparenchymal barrier, the ground substance and the fibrillar elements, chiefly collagen, are affected in antagonistic fashion by chemical substances thereby enhancing the regulator action of this barrier (3). The ground substance is hydrophilic (38) and may store water and electrolytes as well. The extensibility of connective tissue in the living organism depends on its content of water (161), and when water content rises, extensibility increases. In summary, it seems reasonable to state that the origin of the ground substance is still not clearly defined, its turnover, if any, is not known, and its function is still a matter of conjecture.

FIBRILLAR ELEMENTS

Reticulum and collagen.—It was formerly held that collagen could be formed from protein by an enzyme produced by any cell (132), that collagen was formed from fibrin (13, 14), and that collagen was formed in tissue culture in a fibrin-free medium independent of a cell (102). These theories have generally been abandoned following the demonstration by Stearns (178, 179) that, in the transparent rabbit ear chamber, fibroblasts but not fibrin were essential for the production of collagen fibers. In tissue culture, fibrin fibrils bear no spatial relation to the deposition of collagen (81).

The formation of fibrin, a fibrous protein, has been carefully studied, and it has been suggested that collagen may follow a similar developmental pattern (147). Fibrin (from purified bovine fibrinogen and thrombin) has a characteristic electron microscopic structure with an average periodicity of 245 Å (83). Fibrils join laterally to form compound fibers depending on the

pH (at a lower pH of 6.3, the fibers are wider than at pH 8.5), and clotting has been represented as three-dimensional polymerization. Porter & Hawn (146) felt that fibrin is an insoluble fibrinogen without a fundamental change in its molecular plan although it is in a higher state of aggregation. Under the electron microscope, fibrinogen is seen as single, particulate bodies. The fibrinogen molecules are polymerized by the action of thrombin to form needle-shaped, crystal-like protofibrils which then become aligned into fiber strands by lateral association. Thus, thrombin in some way activates the fibrinogen particles to adhere face to face and polarizes them so that at certain points they attach edge to edge.

It has been suggested that collagen is formed by an enzyme present in the ground substance from a soluble polypeptide secreted by the fibroblast (147). By electron microscopy of tissue cultures of fibroblasts, it has been demonstrated that a precollagen consisting of nodular filaments and some larger, finely striated fibrils is present and is believed to represent a stage in extracellular development of collagen (147). The smallest collagen filaments consist of chains of globular protein molecules. The unit fibers or component units of collagen then come together into parallel arrays in a manner similar to that in which the unit fibers of fibrin aggregate to produce large strands of a clot. A finely fibrillar and vesicular structure has been demonstrated in the fibroblast throughout the "hyaline" portion of the cytoplasm. Porter (95a, 148) has recently been able to demonstrate that the early collagen fibril is apparently spun off the surface of the fibroblast. Long bundles of thin fibrils coursing through the fibroblast and usually tending to parallel the free edges have been seen in the electron microscope (15, 77) and may have a part in the production of collagen fibers (95a). Porter (95a) believes the material for the fibril is derived from the plasma gel of the fibroblast and also possibly from the fibroglial fibers. Using osmic acid as a fixative, he has been able to show that the smallest fibril, as spun off the surface of the fibroblast, has a periodicity of 210 Å. After the fibril has been spun off the cell and while it is lying in the extracellular space, every third period seems to enlarge, and the typical collagen spacing of 640 Å develops. Therefore, there seems to be evidence that collagen may be deposited on the surface of the fibril away from the vicinity of the fibroblast (95a).

Upon mixture of solutions of gelatin and chondroitin sulfuric acid and upon acidification (121), a coherent elastic mat of fibers of considerable tensile strength develops. No detailed electron microscopic study of these fibers has been made. It has been suggested that chondroitin sulfuric acid, acting as a multivalent anion, cements together the protein molecules to form fibrous macromolecules and, eventually, fiber bundles (29). In summary, the cell, presumably the fibroblast (77), secretes a precursor, probably a nonfibrous protein (30). With alteration of the physicochemical condition outside the cell, these building blocks tend to associate in a manner similar to that described for rat-tail tendon following increased salt concentration (133).

Collagen has been produced in tissue culture under controlled conditions and is thought to be a secretory product of fibroblasts (81). Granules were seen in fibroblasts near collagen and far away from it. New collagen is not laid down unless fibrocytes (young fibroblasts) undergo proliferation. Lymphocytes take no part in collagen deposition.

A precollagen has been described which is sensitive to cathepsin and papain and moderately resistant to pepsin and trypsin (136). This material has a collagen-like pattern of aminoacids and has been studied with the electron microscope (77, 86). In addition to collagen fibrils, fibrils with axial spacing of about 2200 Å were seen, depending on the concentration of mucoprotein added (86a). Long fibrils or short flat single segments have been observed depending on the pH of the preparation.

During the development of adult rabbit connective tissue in tissue culture, the argyrophilic reticular fibers, believed to be precursors of collagen fibrils, are arranged in parallel, wavy bundles (110). These fibers lose their argyrophilia and stain later as mature collagen (42, 46). Maximow (110) thought the fibrils must be related to cells as they first appeared around cells and fibrin threads of the plasma clot served as pathways for the precipitating material. During wound repair in treated scurvy, collagen is preceded by reticulum (203). It is confined to zones immediately adjacent to the cell body, and its processes include the entire length of the fibroglia fibrils. The course of direction of collagen and reticulum is parallel to the surface of the fibroblast and its processes, never radiating. This finding suggests molecular alignment before the appearance of fibrils (203).

Corium connective tissue fibrils from skin of rats from 2 to 90 days of age have been studied under the electron microscope (76). The argyrophilic reticulum of newborn tissue has the typical electron microscopic appearance of adult collagen fibrils and differs from adult rat skin collagen in being only one-half as wide. With silver impregnation, the silver is bound in colloidal form by adsorption to the reticulum fibrils which become collagen fibers by lateral association, losing their argyrophilia in the process. Chordae tendinae collagen from patients of various age groups was studied by x-ray diffraction (55). Poor orientation of the fibers was seen in young specimens, and all from patients over 45 years of age were found to have a high degree of orientation, indicating a higher degree of alignment of the collagen molecules in the axis of the chordae. The hides of cattle embryos have been examined chemically, and in contrast to adult tissue, only one fibrous protein (reticulin) was found which contained 1.1 per cent sulfur and 6.6 per cent cystine (208). No tyrosine or cysteine was present. In unfixed loose areolar tissue reticulum fibers could not be stretched (54); they either withstood distention or broke.

Astbury (8, 9) has emphasized the two principal groupings of protein fibers: first, the keratin, myosin, and fibrin class, which includes other fibers giving the same wide angle x-ray diffraction pattern; and second, the collagen class, including all forms of white fibrous connective tissue of verte-

brates and others, which also have a characteristic wide-angle pattern. He felt that, since the meridional arc is shorter for collagen than for other proteins, the average amino acid length is shorter because of kinking. Perhaps this kinking is related to the high proline and hydroxyproline content of collagen.

From electron microscope and x-ray diffraction studies, it has been suggested that collagen fibrils are composed of a parallel array of polypeptide chains, each about 10 Å in diameter (77, 81). The chains are of undetermined length, with the amino acids arranged in a highly specific but unknown order. From calculations based on stretching fibrils, the minimum number of polypeptide chains in the collagen micelle has been estimated to be between 24 and 36 (130). Human skin collagen fibrils have an average periodicity of about 640 Å (range, 500 Å to 800 Å) with four, five, and six bands in some periods (73). The possibility has been raised that electron irradiation of the magnitude used in electron microscopy may alter collagen structure (142).

Kanagy (97) has contributed an excellent review on the chemistry of collagen, and a complete bibliography of collagen appeared in 1950 (21). Collagen is a natural fibrous high polymer with little elasticity but great mechanical strength, insoluble in organic solvents, water, dilute acids, and alkalies at ordinary temperature, but with a large swelling capacity in aqueous acids or alkalies in the absence of high salt concentration. There is a characteristic shrinkage of fresh collagen in water at 60° to 65°C.; the length contracts but the fiber becomes wider (98). Fibers so treated are elastic when wet but lose their characteristic x-ray picture. The collagen chain normally exists in a stretched condition. The amino acid composition of collagen is notable for an almost complete absence of aromatic amino acids, a high content of proline, hydroxyproline, hydroxylysine (77), and glycine [which can be incorporated in collagen as N¹⁵-labeled glycine (159)], with little or no sulfur. Thirty-eight per cent of the amino acid residues are polar with an almost equal number of free basic and acidic groups. The minimum molecular weight is 39000 (25). The isoelectric point of native protein of beef tendon is about pH 7.0. At 40° to 60°C., wet collagen shrinks, and at higher temperature, it is converted into gelatin. Heat-denatured collagen (gelatin) has an amorphous appearance under the electron microscope (77), but its amino acid composition is similar to collagen (71). Waksman (195) was unable to bring collagen into solution, and as fine particles, it was poorly, if at all, antigenic. No evidence has been presented to show that gelatin is antigenic. Collagen (the native fiber) is not attacked by trypsin, but at a low pH where the native fiber is disrupted, it is rapidly digested by pepsin. Gelatin is hydrolyzed by trypsin. The actions of trypsin on gelatin occur only on the surface (103), and the action of trypsin on fresh collagen is limited to the cut ends of the fiber. Trypsin cannot attack fibers from the sides. When human skin is treated with trypsin after formalin or alcohol fixation (59), collagen becomes metachromatic. This does not take place with trypsin when the tissue is unfixed. With pepsin, collagen becomes metachromatic even when unfixed.

Rat-tail tendon collagen (131, 164) has certain unusual characteristics in that it is soluble in dilute acetic acid and when dissolved is not visible with the electron microscope. Although the fibrils tend to be frayed at the ends, whereas mammalian skin collagen is rarely frayed, its electron microscopic appearance is similar to the usual insoluble collagen (77). On neutralization of the dissolved acetic acid solution, the fibrils reform promptly and show all the fine structure of native collagen under the electron microscope and by x-ray diffraction (207). These fibrils can be reconstituted in different forms by varying the salt and hydrogen-ion concentration (193). The rate of fiber formation varies directly with the salt concentration and inversely with the hydrogen-ion concentration. With the hydrogen-ion concentration at the isoelectric point of this particular collagen (pH 5.8), it is reconstituted as the original material.

Collagen fibers become oriented, depending on forces of tension, in a manner similar to fibrin (89). In tissue culture, the extent and direction of growth of the collagen fiber represent a response to mechanical tension by orientation along lines of stress (198). Cell orientation and shape are probably secondary to primary orientation of the colloidal matrix in which the cells are embedded (199). Tendon, fascia, cartilage, bone, blood vessels, and skeletal muscle all respond to mechanical tension by orientation of the component cells and intercellular systems along lines of stress (198). Tension is not the only force capable of orientation and aggregation of polar molecules since it is possible that an electrostatic field may do likewise. Piezoelectric forces may play a role in the stimulation of fibroplasia (51, 52, 53).

Elastic fibers.—The third major fibrous element of the connective tissue appears late in embryonal life. The cellular source of elastic fibers is unknown. In tissue culture, these fibers are produced only by tissues which contain them *in vivo* (24). In heart muscle culture, they are most dense when subjected to the pull of pulsating cardiac muscle, but they also form in non-pulsating cultures. The amino acid composition of elastin has been determined (71, 180). Only 1 in 30 of the amino acids are polar [in collagen, 38 per cent are polar (77)]. With aging, there is an increase in aspartic and glutamic acid content, a change in tinctorial characteristics, and an increase in calcium and phosphorus content of arterial elastin (100a). Elastic fibers which are capable of great mechanical strength and long range elasticity, appear in the light microscope as yellow branched fibers or fenestrated laminae and are resistant to boiling water and dilute acids and alkalis. These fibers are not susceptible to recrystallized trypsin (95a) but are hydrolyzed by a crude pancreatic enzyme which may be purified (14b). This purified material has been called an "elastase." Upon exposure of elastic fibers to such a preparation, an opalescent solution appears which separates into a clear solution and a creamy fraction. This creamy fraction contains sphingomyelin, lecithin, cholesterol, and cephalin. Under the microscope, elastic fibers, upon exposure to this enzyme, appear as helically coiled threads. The threads lose their coiling and snap into straight threads, uncoiling meanwhile. Each straight thread then uncoils as two helically coiled threads, and

this process continues until beyond the resolution of the light-microscope [Lansing (95a)].

Under the electron microscope, after 88 per cent formic acid treatment, all formed connective tissue elements except elastic tissue disappear, and the elastic fibers become extended (10). Elastic fibers, when thus extended, separate and appear as linear branching threads which show faint longitudinal striations but no consistent transverse periodicity or spiral arrangement. On neutralization, the fibers resume their elasticity but are too dense for electron microscopy. In trypsin-treated elastic fibers, two entities were observed (75). These had all the components of the molecular model of the elastic fiber proposed by Meyer & Ferri (128) from thermodynamic consideration, namely, a compressed coiled spring held under tension by a stretched elastic band. The findings on electron microscopy have not been confirmed since the coiled threads may have been the result of bacterial (60) or other (78) contamination of the trypsin; however, the lipid of Lansing might act as the stretched elastic band (95a).

In summary, one may infer that the fibroblasts developing from stellate mesenchymal cells deposit ground substance, then spin off reticulum. The reticulum associates laterally into collagen, losing its argyrophilia in the process, with orientation of cells and fibers dependent on mechanical stresses. The origin of the elastic fiber is unknown. Functionally, the fibrous and amorphous elements serve their purpose well. Reticulum acts as a fine meshwork surrounding and serving as a supporting structure for organs and blood vessels. Collagen provides a fiber of great mechanical strength for cohesiveness. Elastic fibers permit long-range elasticity for movement and rebound. The ground substance acts as a medium for transport and for storage of water and electrolytes and, with its gel-like character, also absorbs shocks. Teleologically, an excellent adaptive mechanism for simple support and transport appears to have been evolved.

THE DYNAMIC STATE OF THE CONNECTIVE TISSUE

The dynamic in contrast with the static nature of the living organism has been emphasized (92, 165, 166), and the concept of a turnover of tissue has been evolved. Relatively little work has been done on the turnover of simple connective tissue but from calculations based on excretion studies with N^{15} incorporated into body protein (177), the half-life of proteins of carcass tissues must be almost infinite. In the rat, carcass protein has a half-life of 21 days, while in man it is probably in a much less dynamic state than in the rat. Collagen present in acute and chronic scurvy in the young, growing guinea pig has been estimated and found to be comparable to controls (50, 158). Since new collagen does not appear to be laid down during scurvy, there is no measurable turnover of collagen in the guinea pig for at least 11 weeks. However, the method used for determination of collagen also includes reticulum (95a) which is said by some to be laid down in scurvy (23). This finding has led to the conclusion that, in respect to collagen,

there is constant anabolism with no appreciable breakdown rather than formation and destruction occurring constantly to produce an equilibrium (50). No information is available concerning the turnover of ground substance or the life span of fibroblasts or macrophages.

REPAIR

A major function of connective tissue is the plastic one: the repair of physical trauma after wounds, or that complicated by inflammatory reaction after infections. If the organism survives, the host response is essentially similar after direct physical violence and inflammatory trauma since repair is necessary for ultimate survival. Klemperer (99) has recently reviewed this subject extensively. Baehr & Pollack (11) have described the three types of connective tissue response to trauma: (a) fibrinoid necrosis, (b) fibrillary augmentation leading to sclerosis, and (c) cellular invasion and proliferation (inflammation), or a combination of all three.

Following trauma or inflammation, a substance is elaborated in the damaged tissue [the "leukotaxine" of Menkin (117)] which does not have the biological characteristics of histamine. This material caused an increase in capillary permeability; with this increase, there is an influx into the damaged area of polymorphonuclear leukocytes, lymphocytes and monocytes (macrophage precursors). Apparently, increased capillary permeability is a necessary concomitant to the inflammatory cell invasion. At the area of increased permeability, a substance is elaborated which causes local adhesion of leukocytes to the capillary wall (28a, 206). If trauma is such as to lead to sclerosis or fibroplasia, new fibroblasts soon appear. Shortly after fibroblasts appear, ground substance may be demonstrated by histochemical techniques (95). As reticular and collagenous fibers develop, new blood vessels grow out from capillary buds on pre-existing vessels. Reparative hyperplasia in the skin of the rat has been said to be initiated by the release into the tissues of a metachromatically-staining substance derived from the granules of histogenous mast cells (184). At the site of wound healing, the pH at first decreases and then returns to normal as the process continues to termination (133). The oxidation-reduction potential falls temporarily, and there is an increased concentration of glutathione, of free amino nitrogen, proteolytic enzymes, such as cathepsin (133), and lactic acid (93, 118). A decrease in pH has been found at the site of a fracture in the first stage of the reparative process (94).

Ludford (105) in 1929 stated that

the behavior of cells in the course of wound healing is strikingly similar to that of the cells of a fragment of tissue cultivated *in vitro*. Nevertheless, the factors which regulate cellular proliferation *in vivo* remain obscure.

This statement still applies. One point of contention among histologists is the source of the cells which appear in an inflamed or traumatized area. Polymorphonuclear leukocytes presumably appear from the blood stream,

as do small lymphocytes and monocytes, but dispute has centered about the source of macrophages and particularly of fibroblasts. Maximow & Bloom (111) suggest that macrophages are derived from lymphocytes as well as monocytes and fixed tissue macrophages. Multinucleated giant cells are said to stem from the confluence of epithelioid cells (24) which in turn evolve from macrophages (153). Metchnikoff proposed that the sources of macrophages were lymphocytes, monocytes, reticulum cells, histiocytes, and clasmotocytes [quoted in (153)]. In the inflammatory response to egg albumin in the rabbit (100), the initial macrophage response arises from histogenous macrophages but, when the reaction is at its height, the majority of these cells are of hematogenous origin. The supposed lymphocyte to macrophage transformation is seen only in the first stages of acute inflammation. In the rat, reticuloendothelial cells and fixed connective tissue cells are said to develop into fibroblasts and, following chronic stimulation with trypan blue, no distinction could be made between the reticuloendothelial system and the connective tissue (66). Others believe that macrophages in inflammation and repair are derived solely from wandering tissue cells and from circulating monocytes (12, 80).

Maximow & Bloom (111) maintain that new fibroblasts evolve chiefly from undifferentiated mesenchymal cells lying near blood vessels but may also be derived from macrophages and even from lymphocytes (19, 109). Others claim that new fibroblasts stem from wandering undifferentiated mesenchymal cells (12). (These latter cells are seen infrequently in normal tissue.) Some research workers ignore this problem completely (80). During repair, ground substance and collagen do not materialize until after fibroblasts have appeared (95).

The fibrinoid reaction (fibrinoid change, fibrinoid necrosis, etc.) has been studied extensively (95). This reaction is seen after various types of trauma and may be due to an increase in acid mucopolysaccharide at the site (2). However, there has been some disagreement concerning this interpretation, and it is thought that this reaction may represent only ground substance on which fibrin is superimposed (95). It has recently been shown (97a) that, after chemical extraction, no appreciable hydroxyproline is present, which implies that collagen is not a component of fibrinoid. In various pathological situations in which fibrinoid is found, the appearance of the collagen fibril is unchanged under the electron microscope (62, 205), although admittedly the sampling may have been faulty and the samples may not have been taken from areas involved in fibrinoid.

SCURVY

In the absence of vitamin C, fibroblasts migrate widely (203), multiply rapidly (204), assume the morphology of embryonal connective tissue, and produce a liquid material in lieu of the normal intercellular matrix. No new collagen is laid down (203), and reticulum does not appear until the scurvy is treated, although Bourne (23) has stated that reticulum can be

formed in scorbutic animals but does not mature to collagen. On low doses of ascorbic acid (less than 2 mg. daily), large amounts of reticulum are formed in a wound (33), although the wounds are abnormal in appearance. No metachromatic material is formed during repair in scurvy (141), but with low doses of ascorbic acid, large amounts are laid down. In scurvy, no metachromatic material is seen in regenerating cartilage and it has been suggested that the connective tissue fault in scurvy is due to the inability of the tissues to form chondroitin sulfuric acid (120). The statement that native collagen may retrogress in a scar if vitamin C is subsequently withdrawn (23) is in contrast to the findings reported subsequently that there is no decrease in collagen during the course of scurvy (50, 158). There is disagreement whether vitamin C given locally leads to wound healing in the scorbutic guinea pig (23).

With vitamin C deficiency (23), phagocytosis is inhibited, the differentiation of mesenchymal cells maturing to fibroblasts is delayed, and production of collagen is decreased. It has been suggested that the deficiency may involve cellular phosphatase activity since chemical and histochemical tests show less alkaline phosphatase to be present during scurvy (209). During wound healing in scurvy (202), the epidermis, mononuclear phagocytes (foreign body giant cells are present in both scorbutic and control animals), and the promptness and volume of fibroblastic proliferation are normal, but there are marked changes in collagen production and in the growth of capillaries (112). Mitoses of endothelial cells and capillary buds were observed frequently, but the buds fail to develop into new capillaries. Wolbach & Howe (202) suggested that the failure of cells to produce intercellular substances in scurvy is due to the absence of an agent common to all supporting tissues and responsible for the setting or jelling of a liquid product.

Vitamin C has a late role in the formation of collagen and may effect the polymerization of a simple molecule (204). In tissue culture, a low concentration of ascorbic acid in the culture medium (a nonsynthetic one) failed to modify the amount of collagen or its speed of deposition (81). Embryonal osteogenetic cells, i.e., variants of the primordial stellate cell, were grown in tissue culture: (a) in the plasma of scorbutic guinea pigs alone, (b) in this plasma plus ascorbic acid, and (c) in plasma from guinea pigs treated with vitamin C (149). Little or no collagen formed in the culture grown on scorbutic plasma, in contrast to the amount formed in plasma in which ascorbic acid was present. However, embryonal guinea pig tissue from scorbutic mothers, cultured in the plasma of scorbutic guinea pigs, produced adequate collagen fibers (162). This apparent discrepancy may be related to the fact that the gravid guinea pig on a scorbutic diet develops little or no scurvy; this failure to develop scurvy suggests that the corpus luteum may perhaps synthesize vitamin C (22).

In summary, one may say that in the absence of vitamin C *in vivo*, the fibroblast matures but fails to produce the extracellular components of con-

nective tissue, i.e., ground substance and collagen. Further tissue culture studies are needed to establish this defect *in vitro*.

ANTIBODY FORMATION

Despite a vast amount of research effort, the site of antibody formation remains unsettled (57, 186). In the demyelinating disease of monkeys induced by homologous brain plus adjuvants, a granulomatous lesion at the site of antigen injection is necessary for the development of the typical central nervous system lesion (96). Circulating antibodies are probably produced by the reticuloendothelial system, but fixed tissue antibodies may perhaps result from the reaction of antigen to almost any cell in the body. The experiments on epithelial cells are notably not too precise (57).

SECONDARY AMYLOID

The formation of secondary amyloid is believed to represent a peculiar response of connective tissue to long-continued antibody stimulation (155). Studies on the chemistry of amyloid have not been conclusive, although the mucopolysaccharide is said to be similar to chondroitin sulfuric acid (82). Histochemically, amyloid varies greatly within a single organ; in some situations it is metachromatic, in others it is not. Meyer (126) has isolated a complex mixture of sulfated and nonsulfated mucopolysaccharides from the livers of animals with secondary amyloidosis.

RESPONSE TO X-RAY AND NITROGEN MUSTARDS

Considerable work has been done on the effect of x-irradiation or nitrogen mustards on antibody production (56) and on the connective tissue. With x-irradiation or nitrogen mustard, antibody formation is decreased, fewer lesions occur such as those commonly ascribed to fixed tissue antibody reaction, and serum complement concentration does not decrease (166). In other words, the effect appears to be an inhibition of antibody formation whereas adrenocorticotrophic hormone (ACTH) seems to prevent the development of lesions in spite of the production of antibodies (197). The Schwartzman reaction is decreased when the animal is treated with nitrogen mustard, presumably because leukocytes are necessary to prepare the skin for the sensitizing injection (181). The phagocytic power of the reticuloendothelial system for intravenously injected colloidal gold shows no change after total body irradiation (192). Nitrogen mustard decreases but does not abolish the tuberculin reaction (137). Ox cornea collagen treated with nitrogen mustard is modified chemically and reactively on transplant (145). Actively proliferating tissues, probably at the premitotic phase of cell division, are most susceptible to damage by nitrogen mustard (61).

HORMONAL EFFECTS

Loeb (104) has pointed out that hormones may accelerate or depress the activity of the normal maturation processes in tissue. The work of

Hench, Kendall, Slocumb & Polley (85) on the effect of induced hyperadrenalism on rheumatoid arthritis has served to stimulate the study of the effects of adrenal hormones on the connective tissue. Selye (169), employing several adrenal or pituitary preparations, noted modification of connective tissue reactions characterized by inflammation or fibrosis. During induced hyperadrenalism, fibroplasia is delayed (20, 32, 150 to 152, 175) but not completely inhibited (95). The effects on the reparative processes vary directly with the dosage of hormone administered. The inhibitory effect is apparently upon the cell preceding the fibroblast in development, and a decreased invasion of macrophages into the area has been noted. Once the fibroblast is laid down, in contradistinction to scurvy, collagen and ground substances are deposited; whereas in scurvy (see above) the effect is on fibroblast function after this cell has made its appearance. Cortisone is said to inhibit the incorporation of inorganic sulfate into chondroitin sulfuric acid in the tissues and, during cortisone administration, sulfate is conjugated by liver tissue but not by heart or skeletal muscle tissue (101). Cortisone increases the free hydroxyproline content of brain, liver, and heart in the developing chick embryo (157); a possible implication may be that this amino acid is not utilized in the deposition of collagen under the influence of cortisone. Near a wound, vacuolated cells are seen when the animal is treated with cortisone (114). In the development of a turpentine abscess in the rat, a decrease of fibroplasia is seen with the administration of cortisone (188), and formaldehyde arthritis is inhibited (168).

The effect of cortisone on connective tissue is probably a local one, since local application of the hormone leads to the same delay in the appearance of fibroblasts (26, 88, 91, 171). After long-continued ACTH administration, less proliferating and more mature connective tissue was found in the joint lesion of a patient with rheumatoid arthritis, and the joint fluid reverted to a more normal type (65). Since skin mitoses in the mouse are suppressed by ACTH, the beneficial effect on rheumatoid arthritis may be one of decreased anabolism (72). Tissue slices and tissue homogenates from normal and stressed rats equally inactivate cortisone *in vitro* (139).

There is general depression of lymphatic tissue including a decrease in circulating lymphocytes during induced hyperadrenalism (43). During the administration of cortisone, the invasion of macrophages into an area of inflammation is inhibited (44), even with topical application (45). Fewer macrophages enter the peritoneum in cortisone-treated animals to remove carbon black (176), but this material is phagocytized adequately by the macrophages of the liver (106). After the administration of large amounts of adrenal cortical extract, splenic macrophages phagocytize thorium dioxide (68). In normal rats treated with cortisone, the increased phagocytosis of thorium dioxide involves the spleen and not the liver (69), a situation seen in starvation (70). The systemic administration of ACTH to man is associated with a decrease in the number of large lymphocytes in an area of inflammation (154). In tissue culture, the addition of cortisone is followed by a

decrease in the number of migrating lymphocytes and an increase in the rate of lymphoid degeneration (84). Large wandering cells migrated more in the experimental animal than in the controls, and there was a moderate inhibition of fibroblast growth in some of the experiments. In the concentration used, macrophages were neither damaged by cortisone nor was their phagocytic capacity modified. *In vitro*, cortisone was not cytotoxic against human peripheral leukocytes and did not inhibit chick embryo fibroblast proliferation (14a). The inability of the organism during induced hyperadrenalism to cope with infectious processes has been stressed in brief reports (67, 160, 190). The *in vivo* effect of cortisone on macrophages is apparently one of adequate phagocytosis *in situ* but inadequate invasive tendency.

However, the hyperadrenal reaction may involve the lymphocyte-macrophage-fibroblast system only as a secondary effect; Menkin (116) has shown that adrenal cortical extract inhibits the increased capillary permeability induced by leukotaxine and that adrenal cortical extract or cortisone inhibits the increased capillary permeability caused by an alkaline exudate but has no effect upon that caused by an acid one (119). In rabbit ear windows, vascular tone is better maintained in cortisone-treated animals, and cortisone appears to maintain the integrity of vascular endothelium (52). Sticking of leukocytes to endothelium (margination) is diminished (48, 129). and swelling of endothelium is suppressed (48). The inflammatory lesion in cortisone-treated animals contains excessive amounts of acellular edema fluid, and it has been suggested (67) that this is related to a delay in the diapedesis of leukocytes. Thus, in these studies, it is possible that one effect of cortisone is to prevent the increased capillary permeability associated with inflammation or the elaboration of a substance leading to margination of leukocytes. In isolated surviving carotids of swine, cortisone in very small concentrations has an antihistaminic effect but has no effect on epinephrine or acetylcholine (173). The phosphocreatine and adenosinetriphosphate content of the tissues of adrenalectomized rats maintained on saline or cortisone is similar (1). The administration of cortisone to adrenalectomized and to normal animals is followed by inhibition of the spread induced by hyaluronidase (135). Salicylates, in amounts which have little or no effect on the fibrous tissue reaction, produce even more striking inhibition of hyaluronidase (79).

A substance, presumably elaborated at a traumatized site, produces changes which lead to (a) increased permeability of the capillary wall and (b) a diapedesis of lymphocytes and monocytes through the wall to the injured area. These cells may develop into macrophages and ultimately into fibroblasts. There is a possibility that the elaboration of such a substance is blocked during the hyperadrenal state. Up to the present time, such a possibility has not been investigated directly.

The effect of induced hyperadrenalism on antibody formation has been studied extensively. When the animal is treated with cortisone, there is a decrease in the amount of circulating antibody formed (18). There is no

effect on the passive Arthus phenomenon (58), but inhibition of the active Arthus reaction appears to be due to a decrease in the amount of circulating antibody produced (63, 191). The reactions ascribed to fixed tissue antibody are inhibited if the degree of induced hyperadrenalism is great. There are reports stating that arterial and glomerular lesions developing in animals following foreign protein injections are inhibited by the administration of ACTH or cortisone (16), in spite of the production of antibodies (197), and that passively induced skin hypersensitivity in man is not modified by cortisone (182). In tissue culture, fibroblasts derived from animals sensitized to bacterial antigens are sensitive to these antigens. This sensitivity is markedly enhanced by the local incorporation of small amounts of cortisone into the culture (167). Obviously, in such a problem, there are two variables, the stimulus and the amount of induced hyperadrenalism. The induced hyperadrenalism that is required for modifying an excessive stimulus must be greater than that required for a smaller one. A carefully controlled study varying the stimulus and amount of hormone used is indicated. During the hyperadrenal state, the severity of the scorbutic lesion is decreased (90, 144, 163), this finding may be related to the discovery that during pregnancy scurvy is less severe (22).

Desoxycorticosterone (DOC) increases the number of fibroblasts in a turpentine abscess (187), and an increased fibrous reaction to inflammation follows its administration (169). Given to normal animals, DOC leads to increased fibroblastic activity, increased deposition of metachromatic material, increased amount of reticulum, and decreased amount of collagen (143). In tissue cultures, DOC has a deleterious effect on fibroblasts, potentiated by the addition of cortisone to the culture media (31). The "somatotrophic hormone" of the pituitary has an effect similar to DOC on fibroplasia (170, 188), an effect opposite to that of ACTH. Adrenalectomy abolishes this effect of growth hormone (189). Growth hormone increases the tensile strength of a healing wound (107). The spreading reaction is potentiated by the "somatotrophic hormone," and in this reaction cortisone and DOC act antagonistically (47).

The administration of estrogens and androgens to mice delays the appearance of senile changes in aging articular cartilage (172), and there is a depolymerization of the mucopolysaccharides of the connective tissue of the rat ovary during hormonal stimulation [cyclic changes associated with the estrous cycle (27)]. In a turpentine abscess, estrogen (187) probably mediated through the pituitary (188) causes a decrease in fibroplasia. The secretion of ground substance by mast cells is said to be regulated by pituitary thyrotrophic hormone (4, 5), since in myxedema, in the dermal connective tissue, there is an increased number of mast cells with an increased amount of chromatrophic substance [by chemical extraction, one component of this has been identified in localized myxedema as hyaluronic acid (196)], while in hyperthyroidism there is a dearth of chromatrophic substance.

In summary, cortisone and ACTH apparently decelerate and thereby

inhibit fibroplasia, while DOC and growth hormone accelerate and augment it. The spreading reaction induced by hyaluronidase is inhibited by cortisone and ACTH and enhanced by DOC and growth hormone. Thus, these two groups of hormones seem to have diametrically opposite effects. Cortisone may modify the invasive tendency of macrophages through an effect on capillary permeability and margination of leukocytes, or through its inhibition of the tissue substance usually elaborated at a traumatized site. Through pituitary stimulation, estrogens may act similarly to cortisone, and pituitary thyrotrophic hormone has a rather specific effect on the functions of the mast cell, notably, its tendency to secrete a metachromatic substance. These reported hormonal effects require confirmation but may lead to a greater understanding of the functions of this tissue which is simple morphologically but very complex physiologically.

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PHYSIOLOGICAL EFFECTS OF HEAT AND COLD¹

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ACCLIMATIZATION

The changes which occur in men during acclimatization to work in the heat have been studied again by Eichna *et al.* (1) with an analysis by partitioned calorimetry and calculations of heat transfer. Under the conditions of their experiments, consisting of one-hour daily exposures of men to work in a hot dry environment, the adaptive changes in the men over a period of several days were increased sweating and evaporative cooling and decreased metabolic rate; this resulted in lowered rectal and skin temperature (greatly elevated in the first exposures) and an increased temperature gradient from deep tissues to surface. With the increased gradient, a smaller cutaneous blood flow (70 per cent) sufficed to transfer the metabolic heat to the skin. A similar study using longer daily exposures of the subjects should be made in order to analyze the changes during acclimatization in the heat exchange of men in equilibrium with the environment. A similar analysis of acclimatization to humid heat is needed. The effects of training and acclimatization to hot environments on heat transfer in men have also been studied by MacDonald & Wyndham (2). Improvements in heat transfer, sweating, and temperature regulation in relation to acclimatization were analyzed by these authors in terms of a physical model. In the tropical climate of Nigeria, Ladell (3, 4) found the heat tolerance of residentially acclimatized European soldiers to be greater than that of Nigerian natives of low economic status. Sweat-gland fatigue developed earlier and the chloride content of sweat was lower in the negroes than in the Europeans. These differences are opposite from those reported earlier on the two races in this country where white sharecroppers in the Mississippi delta were found to be less tolerant to work in the heat and to secrete more dilute sweat than the harder working and more prosperous negro sharecroppers [Robinson *et al.* (5)]. In both studies, the differences in the reactions to heat by representatives of the two races were probably due largely to differences in nutritional status, acclimatization, and training and not dependent on racial characteristics or length of residence in the tropics. Mere residence in a hot climate falls far short of acclimatizing men for work in the heat. The salt content of sweat secreted in hot environments is greatly affected by the salt intake of the subject (6).

Galvao (7) found the basal metabolism of residents of the tropics to be more closely related to body weight than to surface area, and on a weight basis, his tropical residents had lower metabolic rates than people of cool

¹ The survey of the literature pertaining to this review was concluded in August, 1951.

climates. The difference was found to be greater for thin and average men than for fat men. He gives evidence that in a warm climate metabolism depends on the weight of active tissue, while in a cold climate the additional heat required for maintaining body temperature brings metabolism into a closer relation with surface area. Radsma (8) also found lower basal metabolic rates in tropical white residents than in residents of a temperate zone, but Daniels *et al.* (9) found no change in the basal rates of the same men during prolonged exposures to cold.

The metabolism of animals is altered under thermal stress (10 to 13), but the role of the thyroid in the adaptation remains a controversial subject. In the acclimatization of rats to air at 5°C., Adolph (10) observed an increase of resting oxygen consumption taking place in 5 to 25 days. Maximal oxygen intake was not modified, and the decrement of oxygen intake occurring with extreme reduction of colonic temperature (15°C.) was not modified; hence these are not factors that undergo acclimatization to temperature stress. Prolonged exposure of normal rats to cold (1.5°C.) caused an increase in metabolism measured at 30°C., and athyroid animals could not survive the cold [Sellers & You (14)]. Thyroxin administered to athyroid rats caused them to survive the cold and to show the increase of metabolism shown by normal rats at 30°C. after acclimatization to cold. Grant (15) found that thyroidectomy increased the tolerance of rabbits to heat stress as evidenced by smaller elevations of rectal temperature and polypnea. He observed a general dulling of thermostatic responses in thyroidectomized animals characterized by low levels of polypnea in heat, and hypothermia in moderate environments. Hoffman & Shaffner (16) found that New Hampshire cockerels (seven to eleven weeks of age) kept for four weeks in a 3°C. environment consumed more oxygen and had heavier thyroids and higher thyroxine secretion rates than birds kept in a 32.2°C. environment. Thyroid glands of chicks from eggs incubated at 36°C. weighed three times as much as those incubated at 39°C. Smith (17) gives indirect evidence of increased thyroid activity in frogs during the summer season.

Recent studies by other methods give data indicating no change in thyroid function in exposure of animals and of man to cold. Using a continuously recording method for respiratory exchange in rabbits, van Goor (18) found that no change was caused by injection of serum from animals exposed to cold or heat. The serum also failed to affect metabolism of isolated brain tissue. Ershoff & Golub (19) found no increase of thyroid hormone in the serum of rats exposed to cold (2°C.) for 45 days. Quimby *et al.* (20), in a series of observations on men and women in the New York area, found that the level of thyroid activity in the euthyroid individual, as determined from the radioactivity of the thyroid gland 24 hr. after a tracer dose of radioiodine (I^{131}), was unaffected by season of the year.

Seasonal variations in the diurnal body temperature curves of young men were studied by Kleitman & Jackson (21). They found the body temperature to be generally lower at all hours of the day in spring than in summer, the dif-

ference being greatest in the minimum temperatures reached in the early morning hours although the temperature and humidity of the air in the sleeping quarters were identical at all times. Daniels (9) observed that cold acclimatization in men was most evident in changed distribution of body heat. Subjective improvement in cold tolerance was present in 11 of 12 subjects. Yoshimura & Iida (22) have observed a seasonal variation of the circulatory reaction in the finger to immersion in ice water, confirming previous reports by Bazett's group and others in this country that acclimatization to cold involves more pronounced cutaneous vasoconstriction in response to cold than is observed in heat-acclimatized subjects.

Blair *et al.* (23) found that cold-conditioned rats and rabbits tolerated eight-hour exposures to -15 and $-40^{\circ}\text{C}.$, respectively, without adverse physiological effects. Unconditioned animals suffered progressive hypothermia and second and third degree frostbite. Scholander *et al.* (11) made similar observations on the arctic gull. Rats exposed to 4° to $6^{\circ}\text{C}.$ developed edema and erythema of the hairless parts of the feet within a few days, symptoms which subsided in from a week to 52 days of continued exposure [Gilson (24)]. Systolic hypertension developed in the rats after several weeks and then disappeared when they were returned to comfortable temperatures. DesMarais & Dugal (25) found that the adaptation of rats to cold is characterized by the establishment of a peripheral blood flow that is represented by a state of slight vasodilation in the skin.

Although work reported in previous years from four different laboratories in the United States and England indicates that during acclimatization of men to work in a hot climate there may be a marked reduction of salt excretion in the sweat and urine brought about by increased activity of the adrenal cortex, Bass *et al.* (26) found no conclusive evidence of altered adrenal cortical activity in man during cold acclimatization. However, other recent experimental work adds to the evidence that the adrenal cortex plays a prominent role in the adaptation of animals to both cold and heat stresses. Sellers & You (27) found that acclimatization of rats to cold before adrenalectomy caused a marked increase in survival time. Gilson (24) observed that adrenalectomized rats exposed to cold developed more severe edema and erythema of the hairless parts of the feet than normal rats. Wertheimer & Ben-Tor (28) found that adrenalectomy of rats before exposing them to cold prevented the increase in glucose utilization and glycogen storage in skeletal muscle occurring in normal animals. Sealander (29) found that exposure of rats to cold caused enlargement of both the adrenal medulla and cortex over control values.

At a location in the desert where a man could survive only two days without water, desert rats were found by Schmidt-Nielsen (30, 31, 32) to thrive on the water content (5 per cent) of dry food plus the water of metabolism. This economical water metabolism was made possible by secreting very concentrated urine (four times the maximal concentration by man) and by limiting to a minimum evaporation from lungs and insensible loss from the

skin by living most of the time in their humid burrows. Kidney function in the dog is not so well adapted to heat stress as kidney function in the desert rat. Pitesky & Last (33) found that both glucose Tm and glomerular filtration rate in dogs were depressed by seasonal heat stress.

Scholander *et al.* (11, 34, 35) have made an important study of the adaptations of birds and mammals to arctic and tropical climates. They give evidence that the phylogenetic adaptation to cold and hot climates by homiothermic animals has taken place largely through factors that regulate the heat dissipation, notably the fur and skin insulation. The body-to-air temperature gradient can be adapted only by means of behavioral thermoregulation (nest building, avoidance of direct sunshine, etc.). They found no evidence of adaptive low body temperature in arctic mammals (except the few hibernators) and birds, or high body temperatures in tropical mammals and birds. With few exceptions, the adults in both climates have basal metabolic rates that fit the standard "mouse to elephant" curve. The critical temperatures of the arctic gull, fox, eskimo dog, and other large arctic animals were found to be in the order of -40 to $-50^{\circ}\text{C}.$; i.e., its normal insulation enables the resting animal to maintain body temperature in these environments without an increase in metabolism above the basal. They would require a 30 to 40 per cent increase in metabolism to keep warm at $-70^{\circ}\text{C}.$, the lowest temperature on earth. The smaller arctic species show high critical temperatures because of their large ratio of surface to mass and relatively low insulation. They must have shelter to maintain normal temperature at rest. Tropical animals and birds, like man, have critical temperatures between 20 and $30^{\circ}\text{C}.$ and are extremely sensitive to temperature changes.

A comparison of the metabolism of excised tissues of the polar cod (adapted to -1.5 to $2^{\circ}\text{C}.$) and the golden orfe (adapted to $25^{\circ}\text{C}.$) was made by Peiss & Field (36). When measured at low temperature (0 to $10^{\circ}\text{C}.$) the oxygen consumption of brain and liver tissues of the cold-adapted cod was several times that of the tropical orfe. This represents an advantageous metabolic adaptation of the cod for life in arctic waters. Freeman (37) found that brain tissue of goldfish acclimatized to cold water metabolized at a faster rate than brain tissue from goldfish acclimatized to warm water when the measurements of metabolism were made at a single temperature. Metabolism of whole animals showed similar responses in relation to acclimatization to cold, an adaptation which contributes to normal activity in the cold environment. Observations by Spoor (38) on goldfish acclimatized to cold water indicate that the erythrocyte count is higher at high temperature than at low.

VARIATIONS OF BODY TEMPERATURE

Studies of regional distribution of temperature in the body are being continued. They add to the evidence that rectal temperature does not necessarily represent average deep body temperature or the temperature of the

thermoregulatory tissues, either on an absolute basis or in its rate of change during adjustments to metabolic or environmental change. Eichna *et al.* (39) measured temperature in the right heart, vena cavae, femoral artery, and rectum in 24 nude subjects at rest in ambient temperatures of 25 to 29°C. They confirmed a point which Bazett had previously stressed, i.e., there is a gradient of increasing temperature in the large veins as they approach the heart. In Eichna's study, the temperatures in the right heart and pulmonary artery were equal and the same as that found in the femoral artery. Rectal temperature was equal to that in the veins draining the liver and brain, and exceeded intracardiac temperature by an average of 0.25°C. under the particular conditions of these observations. In fever, rectal temperature exceeded cardiac temperature by as much as 0.8°C. Mellette (40) found that intravascular temperatures (subclavian artery and inferior vena cava) of men in an air temperature of 21°C. were higher at rest, rose more rapidly to higher levels during work (bicycle ergometer), and returned more quickly to resting levels following work than rectal temperature. Intradermal temperature on the thigh rose rapidly during the first 15 min. of work and, as evaporation increased, gradually declined to the prework level at the end of an hour of work. The difference in the relation of intravascular to rectal temperature of resting men in these two studies must be dependent on the difference in air temperature. Forster & Ferguson (41) found normal variations of hypothalamic temperature in the cat to range from 0.5°C. above to 1.2°C. below rectal temperature.

A study of temperature gradients and heat conductance in the skin of men was made by Hensel (42). In a room temperature of 20 to 22°C., the gradient was from 0.2 to 0.5°C. per mm. at depths up to 1.5 mm. in the skin. By suddenly raising or lowering the surface temperature of the skin, he determined a "heat conduction ratio" for different layers of the skin. Skin temperature of hyperthyroid individuals was studied by Cazzola & Cifu (43). A high percentage of cases showed an absence or inversion of the physiological fall of surface temperature from trunk to extremities. Therapy with thiouracil, by inhibiting thyroid activity and metabolic rate, brought the distribution of skin temperature to the normal range in most cases. Roth & Craig (44) found no relation between hand temperature under constant conditions and basal metabolism of 125 sympathectomized patients who showed reversal of skin temperature between the digits of upper and lower extremities. Kawakami (45) developed an improved thermocouple for measuring skin temperature and is studying the variability of temperature within small areas of skin. Stoll & Hardy (46) have studied the precision of thermocouples as skin thermometers and have described their limitations.

Mental alertness and performance were found by Kleitman & Jackson (21) to be highest at the times in the diurnal cycle when body temperature was highest. Performance on the Link trainer was better in the men who characteristically had higher body temperatures. This suggests that all of us

should begin the day with a brisk walk to raise body temperature and increase circulation before starting work. In a comparison of diurnal temperature variation in men and women, Melette *et al.* (47) found no significant difference in the average maximal values of rectal temperature between the two groups, but lower minimal values were attained in early morning by men than by women. Bigler & McQuiston (48) observed that rectal temperatures of children during general anesthesia and surgery vary widely. Infants under six months old tended to develop subnormal temperatures, and 62 per cent of older children developed fever. Cold water mattresses proved most effective in keeping patients cool during surgery (48, 49). Rubin *et al.* (50) found no significant changes in the rectal temperatures of human males concomitant with a fall in fecal bacterial count. From observations on subjects of different ages, Krag & Kountz (51) concluded that old people are less able to withstand cold than young people are. Their older subjects (57 to 91 years) experienced a greater decline in rectal temperature than the younger ones (22 to 36 years) during exposure to the same temperatures (5° to 15°C.). Oxygen consumption increased more in the older people. Berggren & Christensen (52), applying principles established by Nielsen in 1938, found that the elevation of body temperature in working men can be used to indicate metabolic rate provided the work is continuous and of constant intensity and is not being performed in a hot environment.

Cortisone and adrenocorticotrophic hormone lowered the temperature of the inflamed joints of arthritics in a study made by Hollander *et al.* (53). The authors suggest that measurements of joint temperature may serve as an indication of the effectiveness of antiarthritic agents generally. The joint temperatures of cats exposed to subzero ambient temperatures fell to a greater degree than average skin, body, or muscle temperatures, according to observations by Hunter & Whillans (54, 55). The fall in joint temperature with increased friction probably contributes to decreased efficiency of work done in a cold environment. Dugal (56) found that formaldehyde-induced arthritis in rats was aggravated by exposure to cold.

In birds of all sizes, deep body temperature plotted against the logarithm of body weight gave an inverse linear relation, according to Rodbard (57). Similar data on mammals of 5 kg. and larger gave approximately the same slope, but for small mammals weighing less than 1 kg., each 10-fold decrease in weight was accompanied by a decrease in body temperature of 1.5°C. These small birds and mammals have a high ratio of surface area to mass, and since the mammals are less well insulated than the birds, they require higher metabolic rates in cold environments to maintain body temperatures as high as those of birds. Scholander *et al.* (35) found that small mammals require shelter to survive in arctic climates. Determinations of the mean body temperature of mice exposed to various stresses were made by Hart (58, 59) by measuring the heat content of freshly killed specimens submerged in water in a Dewar flask. By reheating them, he found the specific heat of the mouse's body to be 0.82.

CENTRAL NERVOUS REGULATION OF TEMPERATURE

Heating of the hypothalamic centers by circulating water at 45°C. through silver thermodes fixed in place caused cutaneous vasodilatation in unanesthetized dogs [Ström (60)]. Cooling the hypothalamus by circulating water at 25°C. or below caused cutaneous vasoconstriction only in case the animal's skin temperature had already risen to a high level as a result of indirect heating. Such vasoconstriction did not occur if the circulating water was above 25°C. In no case did hypothalamic cooling cause shivering nor did warming cause panting in the animals, although these responses were elicited readily by reflexes resulting from cooling or heating the skin. Thus Ström found no evidence of a functional importance of cold-sensitive hypothalamic structures regulating skin blood flow or shivering. The temperatures of 45° and 25°C. are both far outside of the usual physiological range of internal temperature regulation. Observations were made by Forster & Ferguson (41) on the normal variations of hypothalamic temperature of cats in relation to thermoregulatory responses. In five of eight cats, panting occurred when the hypothalamic temperature rose above a threshold range during external heating. One of these ceased panting when the hypothalamic temperature was dropped below threshold by introduction of cold water into the stomach, in spite of a continued external heat load. The other animals showed no relationship between hypothalamic temperature and panting. Reflexes, initiated by elevated skin temperature during external heating, cannot be eliminated as the primary cause of panting in these animals—measurements of skin temperature were not reported. The authors found no relation between these normal variations of hypothalamic temperature and thermoregulatory vasodilation and vasoconstriction. Lowenback (61) found that hypoxemia due to occlusion of the carotid or asphyxia caused a rise of temperature in the hypothalamus and a fall of temperature in the cerebral cortex of the anesthetized cat. Polypnea and sweating of the paws accompanied the rise of temperature in the hypothalamus. Other factors than temperature associated with anoxia may have participated in this response.

Slow changes of potential were set up in the anterior hypothalamus of the cat by increasing its temperature, 0.5 to 1 mv. per 0.1°C., according to von Euler (62). The changes could not be obtained by local warming of any other region of the brain or hypothalamus. They could be elicited only by temperature changes and not by changes in arterial pressure or respiration, although there were other centers in the brain stem responding to the latter changes. There was a definite correlation between the slow potentials set up by warming the hypothalamus and thermal panting of the animals. Hall & Whalen (63) observed that elevation of plasma magnesium concentration to 4 to 8 mg. per cent caused polypnea resembling thermal polypnea in the cat. Intracranial procedures preventing thermal polypnea also prevented magnesium polypnea, indicating that heat and magnesium have a common site of action in the brain. Issekutz *et al.* (64) found that the metabolic rates

of the denervated hind legs of dogs were elevated 30 to 50 per cent by excitation of the temperature regulatory center. The response was abolished by narcotics, and the authors concluded that it must be brought about through the blood stream by chemical means. Electrical activity of the cerebral cortex in relation to temperature has been studied in the hibernating hamster by Lyman & Chatfield (65). The arousing hibernator revealed no conspicuous activity in the cortex until its temperature rose to 19 to 21°C. when slow low-voltage activity first appeared. This was replaced at higher temperatures by spontaneous burst activity and at about 29°C. by fast frequency low-voltage discharges. Peripheral movement was elicited at 12°C. by electrical stimulation of the motor areas of the cortex.

Schizophrenic patients showed smaller and more irregular diurnal variations of rectal temperature than normal subjects [Buck *et al.* (66)]. The patients also showed less consistent responses to prolonged cold baths, frequently failing to show the gradual drop in rectal temperature which was typical of normal subjects. Prefrontal lobotomy was found to bring the patients closer to normal in their temperature regulation, indicating that the preoperative abnormality may result in part from a disturbing influence of the prefrontal cortex in lower autonomic centers (67).

TEMPERATURE SENSATION

Recent work by Hensel (68), in which intracutaneous temperature changes at constant external temperatures were measured, showed that under extreme conditions sensations of temperature were still present when the intracutaneous temperature was constant even in the deeper layers. Hensel & Zotterman (69) measured the action potentials in separated fibers of the lingual nerve from cold receptors in the tongues of dogs and cats simultaneously with the tissue temperature. Constant thermal stimuli were maintained by means of a water-circulated metal thermode. At constant tongue temperatures below 23°C., action potentials from the cold receptors continued with constant frequency throughout periods of observation exceeding one hour. Rewarming the tongue to temperatures above 23°C. caused immediate cessation of the impulses. These results support the idea that temperature sensation may be determined by the temperature of the receptors rather than that it is dependent upon changes of temperature. In the constant thermal states of the tissues in these experiments, there was no temperature change, but there was a temperature gradient between the layers of the tongue. Bazett (70) considered that the steepness of thermal gradients in the skin and subcutaneous tissues was the most probable stimulus for both cold and warmth receptors, an idea which is compatible with the above results. Further observations by Hensel & Zotterman (71) on the cat's tongue showed that after-sensations of cold were dependent on impulses from the cold receptors in the previously cooled site which continued only as long as the tissue temperature was below 23°C. These observations indicate that after-sensations of cold are not due entirely to subsequent spread of the low temperature into surrounding tissue.

In studies of sensations of warmth evoked by visible and infrared radiation, Wright (72) observed that the onset of the sensation was gradual and that the rate of development and final intensity depended upon (a) the site stimulated, (b) the intensity of the stimulus, and (c) the size of the area stimulated. The reciprocal of the reaction time was found to vary directly with the intensity of sensation. The threshold for temperature sensation has been found to decrease with increased velocity of temperature change in the environment [Hensel (68)]. Ebaugh & Thauer (73) found that warmth thresholds did not change in relation to varying skin temperatures ranging from 28 to 36°C., results which are not in agreement with earlier studies by Bazett's group. In Ebaugh's experiments, cold thresholds were minimal in cool environments (16 to 24°C.) with corresponding cool skin temperatures and rose steeply to maximal values in warm environments (35 to 40°C.) with warm skin temperatures. In studying the effect of ventilation of an airtight suit on temperature sensation, Thauer *et al.* (74) found that the subject felt cooler than his skin temperature and evaporative loss indicated when the environmental temperature was high, while he felt warmer than he actually was in a cold environment. The explanation was the paradoxically increased or decreased temperature at the inlets of the ventilated suit (feet, hands, and face) in cold or warm environments respectively. Bing & Skouby (75) found an increase in the number of reacting cold spots on the forearm of human subjects with administration of acetyl- β -methylcholine, acetylcholine, and prostigmine. They attributed these changes to a direct effect of acetylcholine on the cold receptors or on the nerve fibers connected with them. Decrease in reacting cold spots occurred with administration of atropine sulfate as well as with epinephrine hydrochloride.

Buettner (76, 77) found an average depth of cutaneous pain receptors of 0.1 mm. and an average pain threshold temperature of 44.8°C. for heat. The threshold temperature was not affected by gradient and was about the same with radiant and contact heat sources. The prepain latent period was decreased in proportion to the initial skin temperature and to the intensity of the radiant source. Burns of first degree occurred very shortly after the pain became unbearable. Heat conductivity of the outer skin did not depend on blood flow except on such areas as the finger tips. Ebaugh, Bird & Hardy (78) observed pain sensation but no temperature sensation in bone marrow when they injected hot (40 to 45°C.) and cold (16 to 22°C.) saline through anesthetized skin and periosteum into the sternal bone marrow cavity.

VASCULAR RESPONSES

The blood vessels in the digits dilate at a lower level of body heating than vessels in the hand and thus play a more sensitive role in temperature regulation. Of the total blood flow through the hand, as measured by a plethysmograph, Greenfield, Shepherd & Whelan (79) found that a greater percentage (69 per cent) passed through the digits of a man when he was comfortably warm at a room temperature of 25 to 30°C. than when he was cool (44 per cent) or when he was heated (44.5 per cent) by being wrapped in blankets

and having both feet and calves in a stirred water-bath at 43°C. However, both the total flow in the hand and that in the digits were much greater when the man was heated than when he was comfortably warm or cool. The same workers observed that upon immersion of the hand in cold water there was an initial vasoconstriction, which almost completely arrested circulation for about five minutes, followed by a cold vasodilation (80, 81). At the height of cold vasodilation of the immersed hand, the heat loss in cal. per 100 ml. per min. was 10 times as great from the index finger as from the entire hand. In these experiments the internal temperature of the fingers immersed in water at 0 to 4°C. fell to values between 20 and 30°C. (82). Bader & Mead (83) observed that blood flow in the fingers of men in equilibrium with a warm environment (32°C.) did not decline when the fingers were cooled by submerging in a bath at -6°C. Vasoconstrictor stimuli (deep respiration, startle, etc.) caused more marked and more prolonged vasoconstriction and reduced blood flow more in the cold fingers than in the fingers of the control hand which remained in the warm atmosphere. The cooled fingers were comfortable in the bath until the occurrence of vasoconstriction, whereupon sensations of cold and pain appeared and lasted until rapid blood flow in the fingers was resumed 2 to 4 min. after the stimulus. These data indicate that blood flow to the hands under these circumstances depends primarily upon the need of the body for conservation or dissipation of heat. On the other hand, the conditions of cold vasodilation observed by Greenfield *et al.* (80, 81) indicate a local vasodilation which provides protection of the member against freezing independently of the general need.

Venous pressure in the feet of men in the erect posture is a result of the relative rate at which the blood flowing into the veins from arteries and capillaries is removed from them by muscular activity. Henry & Gauer (84) found that in adults exposed to hot environments even vigorous walking movements failed to reduce venous pressure in the feet below 70 mm. Hg as compared with 80 to 100 mm. Hg when the men were tilted passively in the erect position. In cool and cold environments, even normal postural movements of the legs and feet reduced venous pressure in the feet to 50 mm. Hg. Elevated venous and capillary pressures resulting from vasodilation undoubtedly play a major part in the development of edema of the extremities of sedentary individuals in hot seasons. Burckhardt & Kunzli (85) found that cooling the skin postponed the erythema from a constant ultraviolet stimulus and that wet skin reacted more strongly and rapidly than dry skin. By spectrographic study, they found that wet skin was more penetrable by ultraviolet than dry skin. Lichter & Schiller (86) studied the time relations of the cutaneous vascular responses including transudation and reabsorption following moderate and intense ultraviolet irradiation.

Vascular reactions in the ears of rabbits in response to general body heating resulted in greatly increased blood flow and a rise in ear temperature due largely to capillary dilation [van Dobben-Broekema & Dirken (87)]. When the blood vessels of the ear were completely denervated, they still responded

by vasodilation to body heating, and blood flow could be influenced by raising or lowering the temperature of the blood to the ear (88). Changes of flow through an isolated perfused rabbit ear with variations of temperature have been explained as being due to changes in viscosity of the perfusion solution and passive changes in the dimensions of the vessels by virtue of their elasticity [Nichol *et al.* (89, 90); Burton (91)]. These authors give evidence that there may be no active response to temperature of the smooth muscle of the vessels in the isolated denervated ear.

Cutaneous vasomotor responses of dogs in a cool environment (15 to 20°C.) to immersion of their hind legs in a warm bath have been studied by Hemingway & Lillehei (92). The vasomotor responses were undulatory in character: vasodilation was transitory in long exposures and often occurred despite a rapid fall in rectal temperature. The vasomotor responses were abolished by sympathectomy, after which thermal regulation in the dog was dependent entirely on shivering and panting. These results are not in agreement with the "central theory" of temperature regulation. Ederstrom (93) observed in anesthetized dogs with spinal cords sectioned at T6 that hyperthermia resulted in greater falls of arterial pressure and of blood flow to the hind foot and intestine than occurred when body temperature was kept normal. In anesthetized animals with unilateral lumbar sympathectomy, blood flow was greater on the intact side at normal temperature, but fell more on this side in hyperthermia. The exteriorized spleen of the mouse was found by Peck & Hoerr (94) to respond to sudden temperature changes with strong initial contractions. At 40°C., the blood flow through the spleen became rapid and constant, and storage in the venous sinuses was eliminated. Lowering the temperature increased the storage phase.

SWEATING AND EVAPORATION

Regional distribution of thermal sweating was studied by Randall *et al.* (95, 96) who observed that, in response to heat, sweating appeared first and most profusely on calf and thigh, next on lower trunk and forehead, and, finally, on the face and upper extremities. There was a reciprocal relation in which sweating progressively increased on the dorsal surfaces of hands and feet and decreased on palmar and plantar surfaces with rising temperature. Takagi & Sakurai (97) studied "hemihidrotic" sweating in a person lying on one side and found that the reflex was elicited by the pressure on the downward side. They mapped distribution of pressure points over the skin surface, finding the axillary region to be the most sensitive to pressure sweating and the outer surfaces of arms and legs and the soles to have no receptors for this stimulation. Peiss *et al.* (98) studied regional distribution of cutaneous insensible perspiration on nude men at an operative temperature of 27°C. Rates of 0.11, 0.05, and 0.04 mg. per sq. cm. per min. were observed on palm, sole, and face respectively, as compared with 0.007 found uniformly on the skin of arms, legs, and trunk. Local insensible perspiration rates correlated with blood flow in the skin in the corresponding regions. Measurements by

Brumshtein (99) of evaporative loss of resting men and women in environments ranging from 5 to 31°C. showed that women evaporated 9 to 21 gm. per hr. less than men under the same conditions. Cutaneous insensible water loss during fever varied directly with changes in the temperature of different regions of the skin in a study by Hildebrandt (100).

Epinephrine and other sympathomimetic drugs caused local excitation of sweat glands of the forearms of men when injected intradermally, although the response was less than that elicited by acetylcholine [Sonnenschein *et al.* (101)]. With a series of experiments in which specific blocking agents were used in combination with these agents, the authors give evidence indicating that the effect of epinephrine and the related substances on sweating is direct and specific. The data do not prove an adrenergic function in the regulation of sweating. In this connection Issekutz *et al.* (102) found that normal thermal sweating was not inhibited by procaine, which blocks the epinephrine response, or by tetraethylammonium chloride, which blocks axon reflexes to the sweat glands.

In the cat, direct electric stimulation of the foot pads produced the sweating response in preganglionically denervated paws, but not after complete denervation [Simeone *et al.* (103)]. Preganglionic denervation increased excitability of the sweat glands to pilocarpine while postganglionic denervation increased sensitivity to pilocarpine for only a few days after which sensitivity gradually decreased. Mock & Julian (104) found in humans that sweat glands responded to pilocarpine one month after postganglionic sympathectomy, but not after two months. Simeone (103) suggested that the delayed decrease in sensitivity serves to distinguish between preganglionic and postganglionic denervation of an area. Kahn (105) used regional sweating and anhidrosis in diagnosing peripheral nerve lesions. Löfgren (106) found that following sympathectomy in man the anhidrotic skin area grew smaller with time, though sweating did not reappear in the entire area within three years. He found no histological difference between the sweat glands of denervated and normal skin regions.

The literature concerning anhidrosis in man was recently reviewed by Shelley *et al.* (107), and he has continued his studies of anhidrosis (108). He was able to duplicate experimentally, following electrolytic injury to individual sweat ducts, four types of obstructive sweat retention which occur clinically in primary or secondary dermatosis. Horne & Mole (109) found that anhidrotic heat exhaustion developing in men in the hot climate of Karachi was not related to salt deficiency. It has been generally believed that "sunstroke" and "heat stroke" are identical and that the sun acts only by increasing the heat load. There was little evidence of specific effects of sunlight contributing to heat stroke until the work of Thomson (110) who found that in hot humid environments ultraviolet radiation in moderate erythematous doses reduced by 60 per cent the sweating responses of men to a standard indoor heat load on the second or third day after exposure to the radiation. After recovery, a second exposure produced a further reduction in sweating.

The effect was found to be due in part to blockage of the sweat gland ducts resulting from a vesicular rash (111). There was evidence that the secretion pressure of the sweat glands was reduced, indicating that secretion itself was diminished. Locally applied acetylcholine did not cause a return to normal of sweating after radiation. Folk & Peary (112) found that an impermeable barrier in the footwear decreased sweating and insensible perspiration of the feet in men both at rest and in marching in both cold and warm environments. During eight-hour field tests, the accumulation of moisture in the footwear was 60 per cent less when an impermeable barrier was worn outside the first sock than when it was worn outside a fourth sock and just inside the shoepac (113). Moisture accumulation in the footwear decreased its insulation and therefore the comfort of the men in cold environments. The mechanism of the reduction in sweating has not been explained.

Recent reports in the literature add further evidence of the variability in the composition of sweat. Van Heyningen & Weiner (114) found the concentrations of chloride, urea, and lactic acid always to be greater in sweat collected from the arm and hand than in sweat from the exposed general body surface. The proportion of chloride to lactate increased with environmental heat stress. Acclimatization to heat was accompanied by a reduction in lactic acid concentration in sweat from 300 to 100 mg. per cent (115). Ottenstein (116) found that apocrine sweat was more acid and contained a greater concentration of ammonia than eccrine sweat. Lactic acid concentration varied from 247 to 336 mg. per cent, values similar to those observed by Weiner (115) in unacclimatized subjects. Children with nephrosis given a thermal stimulus have been found to secrete only one-tenth to one-fifth as much sweat as normal children [Warming-Larsen & Wallace (117)]. In nephrosis, the sodium chloride concentration of their sweat was three to six times that of normal children, and the potassium concentration was reduced to one-half normal. Johnston *et al.* (118), in observations on women exposed to heat stress, found that the mean loss of iron in the sweat ranged from 0.06 to 0.48 mg. per hr. in four subjects and calcium loss was from 4 to 14 mg. per hr. The loss of iron in the sweat was not related to the amount in the diet.

Variation in the sodium chloride concentration of sweat of normal men may range from 5 to more than 100 meq. per l. The concentration may be related to individual differences, but it also may vary from time to time in the same individual and may even differ in samples of sweat collected simultaneously from different skin regions of the same man. Some authors have ascribed the variations in the same individual to acclimatization to a hot climate accompanied by increased activity of the adrenal cortex, others to changes in the salt balance of the individual, and still others to differences in skin and rectal temperature and to the rate of sweat secretion. Experiments by Robinson *et al.* (6, 119) and by Locke *et al.* (120) give direct evidence concerning the factors responsible for the variations found in the same individual. In observations made by Robinson's group on men working during exposures to severe heat stress, when each of a man's hands was kept at a

different temperature simultaneously, the sodium and chloride concentrations of sweat collected from the cooler hand were always significantly lower than in the sweat from the warmer hand. The salt concentration in sweat from a single hand was raised or lowered within 30 min. by raising or lowering the hand temperature. Evidence is given that this effect of temperature on sweat chloride was directly on the sweat glands and not due to central or hormonal control. Locke *et al.* (120) found, in exposing subjects to varying heat stresses, that the chloride concentration of hand sweat varied directly with the rate of sweating if local skin temperature and hormonal factors were constant. They also confirmed previous reports in the literature that adrenal cortical activity is a determining factor in regulating salt concentration in the sweat. They give evidence that the ratio of sweat chloride to the rate of sweating may be an index of adrenal cortical activity. Reports in the literature show that when unacclimatized men perform daily work in hot environments and sweat rapidly, they may or may not show a gradual decrease in chloride concentration in the sweat over a period of several days of acclimatization. Robinson *et al.* (6) present evidence that a reduction in chloride concentration in the sweat with acclimatization depends upon the development of a salt deficiency due to excessive loss of salt in the sweat by the subject. When intake was sufficient to prevent a salt deficiency, the concentration in the sweat was not reduced. Present knowledge on the subject leads us to the conclusion that the dominant regulatory factor in determining the salt concentration of human sweat, as well as its loss in the urine, is the hormonal activity of the adrenal cortex which is elicited in response to salt deficiency. Alterations of both the skin temperature and the rate of sweating may directly affect the concentration of salt in the sweat but to a lesser extent than the adrenal cortex does.

SPECIAL METABOLIC EFFECTS

Ketonuria has been found in soldiers during arctic field trials. Sargent & Consolazio (121, 122) observed that the ketonuria (*a*) declined with training and acclimatization, (*b*) was highest in the men who worked hardest, and (*c*) increased during moderate caloric deficiency. Molnar (123) found ketonuria in men during arctic bivouac but never in the same men during temperate bivouac. Other investigators have previously found that exercise-ketosis may be prevented by administration of glucose or adrenal cortical extract during the work phase. Fundamental investigation of the phenomenon is required before an interpretation of the effects of stress, training, and acclimatization on ketosis can be made.

You *et al.* (124) found that increased excretion of nitrogen in the urine occurred when rats were exposed to cold and presented evidence that the increase was not dependent on the presence of either the adrenal or the thyroid glands. Rodbard & Goldstein (125) found that blood sugar in the intact chick rose and fell with body temperature. This thermoglycemic re-

sponse was blocked by abdominal vagotomy but was unaffected by pancreatectomy. In a study of the effect of temperature on the oxygen consumption of rat heart slices, Fuhrman *et al.* (126) made measurements of the Q_{O_2} between 10° and 42.5°C. and found the optimal temperature to be about 38°C., which is lower than the optimum previously found by the same authors for other rat tissues (brain, kidney cortex, liver, skeletal muscle). Jasper & Archdeacon (127) studied metabolism of excised brain and liver tissues of the rat at temperatures between 37 and 42°C. A marked increase in metabolism was shown by liver tissue at 41°C. and by brain tissue at 42°C.

Nutritional requirements are seriously affected by thermal stress. In animals exposed to cold, increased requirements of thiamine (128) and riboflavin (129) have been reported. Deficiencies of vitamin A (132, 133) and thiamine (134) have been found to impair the ability of animals to withstand cold. Retarded development of young rats in prolonged exposure to cold was observed (135) and the retardation was prevented or corrected by supplementing the diet with the known B vitamins. Arthritis in adult rats was aggravated by cold and diminished by administration of ascorbic acid (56, 136). Pagé & Babineau (130, 131) observed, in rats exposed to cold, hypertrophy of the brown adipose tissue and an even higher rise in its ascorbic acid content. The authors suggest that ascorbic acid is intimately linked with fat metabolism. Bacchus *et al.* (137) give evidence that the protective action of ascorbic acid against cold stress in rats requires the presence of the adrenals.

MISCELLANEOUS EFFECTS OF HEAT

Buettner (76) reported that the temperature change of skin, suddenly heated or cooled, is subject to the physical laws of heat conduction and heat transfer and that causation of burns can be predicted from the curves of temperature change. He also studied the protection from intense radiant heat flash afforded by aluminum-coated clothing (138). A study of evaporation and heat exchange from the lungs and air passages of men exposed to high air temperatures (49 to 93°C.) was made by McCutchan & Taylor (139). The temperature and humidity of expired air were described in relation to temperature and humidity of the inspired air. Stoll (140) found the operative temperature in Death Valley to be about 30°C. higher than, and radiant heat load on man as much as 25 times, that experienced in New York City.

The effects of heat stress on the ability of men to carry out simple mental tasks were investigated by Blockley & Lyman (141). Decrement in performance below the level established immediately prior to heat exposure, if it occurred, began to appear at approximately the same time that the physiological state of the individual showed deterioration. Blood leukocyte response following fever induced by a fever cabinet or by pyrogens was found by Kirkendall *et al.* (142) to simulate that seen after administration of ACTH, although the uric acid-creatinine ratio and corticosteroid excretion were not altered in the fever as in response to ACTH liberation. Additional

evidence is required to prove that ACTH release is increased in fever. Ducommun (143) found that cortisone antagonized completely the hyperthermia caused by dinitrophenol in rats.

Murphy *et al.* (144) irradiated the hind limbs of adult dogs with currents of six different wave lengths. With the shorter electromagnetic waves, the temperature elevation was greater in the superficial tissues than in the deeper tissues. The long wave lengths were more effective for deep tissue heating. Nelson *et al.* (145) found ultrasonic radiation the best source of energy for selective heating of bone cortex and bone marrow in dogs.

HYPOTHERMIA

In men seriously chilled by immersion in cold water, Behnke & Yaglou (146) found that cold shock during the first stages of rewarming in air at 21 to 38°C. was greatly prolonged and even more distressing than the initial immersion shock. Rapid rewarming in water at 38 to 40°C. prevented the agony of chills and the precipitous after-drop of deep temperature. By calculations of heat exchange, Glaser (147) estimated that survival of a man exposed to cold water would be greatly prolonged if he would swim at a moderate rate until exhausted. The rate of cooling of anesthetized dogs immersed to the neck in an ice bath was decreased by even slight surgical maneuvers, possibly through adrenal activation—increasing metabolic rate by epinephrine secretion or evoking stress response of the cortex. Cooling rate was also decreased by long hair, shivering, and increased body size (148). Coronary arteriovenous oxygen difference in dogs cooled to 20°C. was found to be normal, indicating no serious cardiac hypoxia results from the shift of the hemoglobin dissociation curve in the cold [Penrod (149)]. Bigelow *et al.* (150, 151, 152) have made some interesting studies of hypothermia in cardiac surgery. By lowering dogs' temperatures to 20°C. and occluding the vena cavae, they were able to exclude the heart from the circulation for 15 min. for surgery with a good percentage of recovery. Lessen & Demeester (153) observed that in dogs under anesthesia, hypothermia caused a lowering of arterial pressure and depression of reflexes from the carotid sinus with a return to normal when the central temperature was raised again. Vagotomy increased hypothermia of pigeons immersed in cold water [Cacioppo & Buzanca (154)]. Lethal body temperature in chickens was found to vary from 15°C. in one-day-old chicks to 23°C. in adult birds [Moreng & Shaffner (155)].

Changes occurring in hibernating animals have been studied by three groups of investigators. Chatfield & Lyman (156, 157) found that in the hamster the waking process from hibernation was initiated with the following physiological changes: increase in heart rate, slow at first and later linear with the increase in body temperature; abolition of atrioventricular dissociation if present; increase in velocity of conduction of the cardiac impulse; increase in arterial pressure; cutaneous vasoconstriction; activation of skeletal muscles; and increase in oxygen consumption. Chao & Yeh (158) found

that the hedgehog in hibernation had a body temperature 1°C . above ambient temperature when the latter was above 0°C . and that the animal's freezing point was -0.5°C . Upon arousal there was an initial slow rise of body temperature to 18°C . followed by a rapid rise between 18 and 27°C . Hock (159) found that bats' body temperatures quickly fell to that of the environment every time they came to rest and that by muscular activity they could quickly raise body temperature above the hibernating temperature. Perkins *et al.* (160) presented evidence that cooling as a stimulus to smooth muscle either acts on a different excitatory system than epinephrine or acts directly on the contractile mechanism.

COLD INJURY

From data on the velocity of fall from aircraft and rate of freezing at different altitudes and temperatures, Webster & Smedal (161) calculated that the maximum altitude from which a man can free-fall without frostbite of bare skin areas is 39,600 ft., while with a 28-foot parachute open, the maximum altitude is 20,910 ft. Yoshimura & Iida (22) found that the "resistance index" to frostbite, based on skin temperature reactions of the finger submerged in ice water, varied among individuals and that the index of the same individual varied with the season, with ambient temperature, with exercise, and with meals. The Randolph Field group produced varying degrees of local cold injury in rabbits by immersing one leg for 30 min. in alcohol baths varying in temperature from 5° to -40°C . (162). Skin and muscle necrosis following cold injury were definitely decreased by rapid and prolonged rewarming in water at 42°C . (163). Hypoxia following severe cold injury increased the extent of tissue loss considerably (164). Cold injury to the leg resulted in acute renal tubular degeneration (165). The weight of the adrenal cortex increased in direct relation to the degree of cold injury, and this was accompanied by a decrease in body weight (166). In severe cold injury degenerative changes of the adrenal cortex, which were increased in severity by heparin treatment, were observed. Hurley *et al.* (167) found that the dihydrogenated ergot alkaloids were of value in treating frostbite, the effectiveness being due to their vasodilator action. Hunter *et al.* (168) observed no benefits from the use of trafuril, an ester of nicotinic acid, in preventing frostbite of the human hand.

GENERAL STUDIES

The "Effective Temperature" (ET) index has been investigated by Glickman *et al.* (169) using as criteria of the effect of the environment, temperature sensations, skin temperature, rectal temperature, heart rate, and evaporation. Their data indicate that, except at high temperatures, the present ET index is adequate when subjects pass back and forth between different environments. Their results on men in equilibrium indicate that ET places too much emphasis on the influence of relative humidity. Ellis (170) reviewed papers on the maximum stress imposed by hot climatic conditions

under which a man can exist or work with varying degrees of efficiency. His review includes a description of the climatic chambers of the Tropical Research Unit at Singapore. Lee & Pendleton (171) and Lee (172) set forth the principles that should guide the mode of living and working of tropical residents and the provision of housing suitable for humid tropics. Mitchell (173) outlined the effects of environment in studies of nutrition.

Brody and his colleagues (174, 175) have made a significant study of the effects of temperature (0 to 105°F.) on the metabolism, feed consumption, milk production, body weight, body temperature, respiration, evaporation, and pulse rates of Brahman (evolved in India), Holstein and Jersey (evolved in Europe) cows. The Brahman cows were more tolerant of heat than the European breeds, presumably because of their greater surface area per unit weight and their lesser total and basal metabolism. On the other hand, the larger Holsteins were not affected by lowering the temperature to 0°F., while the Brahmans increased their feed consumption and heat production by 50 per cent and the Jerseys by 30 per cent. The ratio of evaporative cooling to total cooling (or total heat production) was about the same in all animals. The authors suggest that open pen-type barns suffice for sheltering productive cattle against cold, but that special devices are needed to protect them against heat. Badreldin (176) studied heat tolerance in Egypt in buffaloes, native Egyptian cattle, and European-evolved shorthorns and Jerseys. He found the buffaloes most tolerant and the shorthorns least tolerant to heat. Detailed reports of climatic problems in livestock production were made at recent meetings of the Food and Agriculture Organization of the United Nations (177, 178).

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ENERGY METABOLISM OF BIOSYNTHESIS AT THE CELLULAR LEVEL¹

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INTRODUCTION

Scope and purpose.—The previous reviews on the subject of energy metabolism in the present series have emphasized either in part or exclusively the intact animal and its component parts, in terms of tissues and organs. The present review will concern itself exclusively with the problem of energy metabolism at the level of the individual cell and its component parts, in terms of enzymes and aggregates of enzymes.

The synthesis of every cell component and the performance of every cell function involves the expenditure of energy. Consequently, an exhaustive treatment of cellular energy metabolism is impossible, even were the reviewers to confine their literature coverage to a very limited period of time. Any attempt at a rational synthesis or critical analysis of a subject of this diversity necessarily involves the selection of the important and the pertinent. It is the purpose of the present review to summarize the present status of the research on that portion of energy metabolism which seems likely to be of future fruitfulness in attempts at understanding the nature and function of the intact living cell. It need hardly be added that questions of importance and pertinence are ones relative to the peculiar bias of the reviewers. Under the circumstances, a precise indication of the period covered is not too informative. Nevertheless, it may be noted that the period from July, 1949 to May, 1951 has been the one on which most attention has been concentrated. Contributions preceding this period are included whenever the development of the origin or continuity of a concept made it seem desirable to do so. Lack of space and a desire to present a unified treatment of at least one phase of the problem has forced the authors to omit considerations of functional cellular physiology in order to concentrate on the relation of biosynthesis to energy metabolism.

The following common abbreviations have been used: ADP and ATP for adenosinediphosphate and adenosinetriphosphate, TPN and DPN for triphosphopyridine nucleotide and diphosphopyridine nucleotide, and TPNH₂ and DPNH₂ for their reduced forms.

¹ The survey of the literature pertaining to this review was concluded in May, 1951.

The concept of energy metabolism.—The accumulating evidence from biochemical research has made more and more untenable the concepts of a dichotomy between catabolism and anabolism. The eventual disintegration of this concept, held by the earlier generations of physiologists and biochemists, was prophetically foreshadowed by Kluver (1) in a book which represents the first explicit enunciation of the principles of comparative biochemistry. In this penetrating analysis, Kluver pointed out that the essence of the biochemical reactions going on in living cells can be summarized in an equation of the following type (or one of its variants): $AH_2 + B \rightleftharpoons A + BH_2$. It is evident that this equation could equally well describe the catabolic degradation of AH_2 to A or the biosynthesis of BH_2 from its precursor B. This simple statement pointedly emphasizes the impossibility of deciding, without arbitrariness, whether a particular reaction is catabolic or anabolic. The ensuing 20 years of biochemical research have amply attested to the value of this prophetic insight which adopts the view that it is more fruitful to regard these seemingly opposite kinds of biochemical events as two different aspects of one and the same biochemical process.

The year 1941 witnessed the appearance of Lipmann's (2) and Kalckar's (3) classic papers on the significance of the phosphate bond. The work of many biochemists was synthesized into a coherent picture of energy transport and utilization and concrete chemical meaning was given to the concepts implicit in Kluver's formulation. Lipmann made it clearly evident to all that the problem of the synthesis of a compound C from its two component parts A and B could not be artificially separated into two distinct questions: one involving the nature of the reactants, and the other relating to the question of the energy input mechanism required to put the two components together. The idea was developed that energy requiring synthetic steps are converted into spontaneous reactions by supplying the necessary energy in the molecular structure of one of the reactants. This concept unified and simplified the problem of biological synthesis and focused attention on the energetics of group transfer. The ideas developed by Lipmann in this and subsequent papers (4, 5) have had a profound influence on the research of the last decade. The results obtained serve to emphasize the brilliance of this accomplishment as well as its general validity.

ENERGY ACCUMULATION

Glycolysis.—In recent years, investigation of the energy generating mechanism of glycolysis has shifted to problems of regulation and interaction between the various enzymatic and coenzymatic components of the glycolytic system. Meyerhof & Wilson (6 to 9) have demonstrated that one of the key regulating mechanisms in the glycolysis of cell-free extracts is the activity of adenosinetriphosphatase and its effects upon ATP:ADP ratios. Racker & Krinsky (10) exhibited the situation where the regulatory breakdown occurred at the point of ATP generation in the presence of ferrous sulfate. Recent work by Stoesz & LePage (11) supports earlier views that

the initial steps of glucose phosphorylation are usually the limiting ones in glycolysis. A cozymase derivative (12) and a nucleotide-like factor (13) have been reported to influence the glycolysis rates of yeast extracts.

Aerobic metabolism.—Our knowledge of how the oxidative energy of (C—H) cleavage is preserved in the anhydride C—O—P link is quite satisfactory in the case of anaerobic dismutations. The same cannot, however, be said for the coupled oxidations effected by the aerobic pathway.

Many facts indicated that the succinic oxygen system was more complex than the combination of succinic dehydrogenase, cytochrome-*c*, and cytochrome oxidase. It was also evident that we were not in a position to interpret with any precision the relation between this latter system and the dehydrogenases which function via DPN and diaphorase. A major advance in our understanding of the hydrogen transport in these systems and their relations to one another have been made as a result of a series of papers by Keilin & Hartree (14) and Slater (15 to 21). British antilewisite (BAL) was used to dissect this system and it was found that a hitherto unknown factor, sensitive to BAL, functions as a common link between the various systems. This factor operates between cytochrome-*b* and cytochrome-*c* of the succinic system as well as between diaphorase and cytochrome-*c*. These observations can be summarized in the following picture of hydrogen transport:

Substrate-dehydrogenase → DPNH₂ → diaphorase → methylene blue → O₂

Slater's factor → cytochrome-*c* → cytochrome-*a* → cytochrome-*a*₃ → O₂

Succinate-succinic dehydrogenase → cytochrome-*b* → methylene blue → O₂

Slater (21) presents evidence which suggest a specific association of cytochrome-*b* with the oxidation of succinate and inclines to the belief that succinic dehydrogenase and cytochrome-*b* are identical. According to the above mechanism, methylene blue shunts the hydrogen transport system of the DPN-diaphorase mechanism away from Slater's factor, and thus a series of oxidations which could be coupled with phosphorylations do not take place. This is in agreement with both the observations and interpretations of Lehninger (22) who reported that methylene blue could uncouple phosphate esterification from electron transfer and suggested that it did so by shunting hydrogen transport away from the cytochrome system.

GEOMETRY AND ENERGY GENERATION

Of all the fields of research on energy pathways, that of aerobic oxidations has demonstrated most dramatically the need for geometrical concepts in thinking about enzyme function and interrelations. We have had the Krebs tricarboxylic acid cycle available as a fruitful guide for 12 years, and it has served admirably in the integration of the vast amount of information which has accumulated concerning aerobic oxidations. Further, as a result of the ingenious efforts of Ochoa and his collaborators, as well as many other workers, a majority of the enzymes postulated by the tricarboxylic acid

mechanism have been isolated in soluble form and their properties studied. The results of these admittedly striking advances have been summarized in a recent stimulating review by Ochoa (23). Despite the marked progress which can be recorded, it nevertheless remains true that the system required for the complete oxidation of pyruvate to carbon dioxide and water has not thus far been reconstructed from the component enzymatic and coenzymatic parts. Comparison of the isolated component systems with cruder preparations (e.g., with regard to the efficiency of coupling of the oxidations with phosphorylations) has forced some workers to the conclusion that the properties of a given enzyme while still a part of a complex are different from those which it exhibits in isolation. The concept of "multi-enzyme systems" has emerged as a result to describe the behavior of a group of enzymes functioning as a unit. A discussion of analogous concepts from the point of view of soluble enzyme systems is to be found in Dixon's recent book (24).

Geometrical complexity at the enzyme level.—An interesting instance of structural complexity at the level of a single enzyme molecule has been encountered by Ochoa and his collaborators (25). An enzyme ("malic") can be isolated from pigeon liver which can carry out the oxidative decarboxylation of malic acid to pyruvic acid and carbon dioxide in the presence of TPN. This reaction requires two discrete biochemical events, one involving the oxidation of malic to oxaloacetic, and the other the decarboxylation of the oxaloacetate to pyruvate and carbon dioxide. Yet, apparently a single enzyme can perform both of these functions. Interestingly enough, separation of these two catalyzed events on different enzyme molecules leads to the disappearance of the reaction. Thus, it was found that a combination of purified malic dehydrogenase and oxaloacetic decarboxylase with added cofactors failed to give the reaction mediated by the "malic" enzyme. Here, then, we have an instance in which the active sites participating must be geometrically arranged on a single "double-headed" enzyme molecule, presumably to effect a more efficient utilization of the intermediate substance.

Geometrical complexity at the particulate level.—Of great physiological interest was the emergence of more involved geometrical complexities from attempts at understanding the over-all oxidative mechanisms of tissues and homogenates. It has been known for some time that the oxidative capacity of a tissue homogenate is associated in large part with easily sedimentable particles. Recent work by Schneider & Potter (26) and by Kennedy & Lehninger (27) has identified the particulate elements concerned with the mitochondria of the cytologists.

Much of our recent information concerning the enzymatic nature of these particles has come from the laboratory of Green (28 to 32) and has been reviewed by him (33). Lehninger (27, 34 to 36) has also made important contributions in this field, which he has reviewed (37). Green came across this system in attempts at studying the oxidation of pyruvate to acetate. It was soon discovered that the preparations used were carrying out the complete oxidation of pyruvic acid to carbon dioxide and water via the tri-

carboxylic acid cycle, and all attempts at separating out the partial system of interest failed. Green and his co-workers deserve a major share of the credit for realizing that this enzymological nuisance could be converted into a blessing. They realized that this system could as legitimately claim the attention of the enzymologist as do purified isolated enzymes, and they concluded that they were dealing with an integrated system and not with an indiscriminate mixture of enzymes. The uniqueness of this system as a unit of function was formalized in the term "cyclophorase" (28). Initially, the concept embraced principally the existence of the set of tricarboxylic acid enzymes as an integrated functioning unit. Subsequently (33), it was broadened to include the concept of any complex of integrated enzymes that confers properties on the component enzymes which these would not possess in isolation. It was soon found (30) that suitably prepared particles contained large amounts of bound coenzymes including DPN, TPN, flavin adenine dinucleotide (FAD), and diphosphothiamine. Experiments (32, 38, 39) with P^{32} showed that the particulate system contains an extremely labile phosphorus (gel-P), which cannot be removed by washing with water but can be released by trichloroacetic acid.

Lehninger and his co-workers (40, 41, 42) have made important recent contributions to our understanding of the phosphate metabolism of such mitochondrial preparations. In these experiments, β -hydroxybutyric acid was employed as the most suitable substrate since the preparation could not oxidize acetoacetate. It was established that the oxidation was coupled to phosphorylation, and the first relatively direct experimental evidence was thereby provided for the theory enunciated by Lipmann in 1946 (4) linking the oxidation-reduction of the coenzymes with phosphate esterification. Final confirmation of this was recently provided by Lehninger (43) in a most significant paper which provides direct demonstration that orthophosphate uptake is coupled with the oxidation of $DPNH_2$. It was further shown (44) that $DPNH_2$ can replace members of the tricarboxylic acid cycle in initiating the oxidation of fatty acids by the mitochondrial preparations. Hunter (45) and Hunter & Hixon (46), using particulate preparations from liver and kidney, were able to demonstrate phosphate esterification coupled to anaerobic dismutations involving α -ketoglutaric with oxaloacetic and ammonia.

In addition to carrying out coupled oxidations with members of the tricarboxylic acid cycle (28, 47), such particulate preparations can completely oxidize fatty acids (48), fatty amines, and fatty aldehydes (33), L-proline (29), L-alanine (49), L-glutamate (50), and D-aspartate (31). Evidence is further accumulating that the particles can employ the phosphate bond energy that they generate for synthetic functions. Cohen & McGilvery (51) early described a particulate system obtainable from both kidney and liver which was capable of condensing lysine with benzoic acid to form hippuric acid. This was subsequently confirmed by the more recent work of Kielley & Schneider (52). Leuthardt & Muller (53) indicate that the first step in the synthesis of urea takes place in the mitochondria. Borsook (54) presents and

reviews evidence for the incorporation of amino acids in the mitochondria. Finally, we may note the experiments of Friedkin & Lehninger (34) which demonstrated the ability of these elements to incorporate P^{32} into phospholipid, nucleic acid, and an unidentified "phosphoprotein" fraction.

Autonomy of the particulate systems.—The efficiency of the coupled oxidations carried out by these particulate elements and the varied types of synthetic activities they possess raise the question of their autonomy. The biochemical literature surveyed in the preceding section suggests that these particles, rich in ribonucleoprotein, might well possess an enzymatic apparatus of sufficient complexity to synthesize their component parts.

From the biological point of view, the question of autonomy is discussed in terms of transmission and the capacity of self-reproduction. A series of papers remarkable for both their content and ingenuity have recently appeared from the laboratory of Ephrussi which provide concrete and pertinent data relative to the question of the biological autonomy of cytoplasmic particulate elements. A mutation in yeast was discovered (55) which occurred spontaneously and could be induced with extraordinarily high frequency by treatment with acriflavine. The mutant cells were characterized by a very slow growth rate which was found to be due to the absence of the aerobic pathway (56, 57). A genetic analysis (58) of this mutant revealed surprisingly that the biochemical deficiency was apparently not under gene control, since back crosses of the mutant to the wild type invariably gave four wild type spores instead of the expected 2:2. The absence of chromosomal control over the transmission of this character in such mutants was further indicated by single cell analysis of progeny derived from acriflavine-treated cells (59). The pattern of mutant progeny obtained was one that could not easily be explained on a genic mutation basis but was one which would be expected if the character was determined by cytoplasmic particulate elements which were being randomly distributed during cell division.

Slonimski & Ephrussi (56) showed that the respiratory deficiency in these mutants was due to the absence of cytochrome oxidase and succinic dehydrogenase. An analysis of the particulate fraction derived from such mutants revealed the absence of mitochondria containing cytochrome oxidase and succinic dehydrogenase (60). It is of interest to note that the mitochondrial fraction did contain cytochrome-*c*. Cytochrome-*b*, however, was missing, which is consistent with Slater's interpretation (21) of the identity of the succinic dehydrogenase and this particular cytochrome.

The weight of the evidence provided by these workers strongly supports the existence of a heterogeneous population of cytoplasmic particulate elements which are randomly distributed during cell division and which can be associated with the mitochondria. A high degree of biological autonomy, which may be a reflection of their varied and complex biosynthetic capacities, is therefore indicated for these particulate elements. It is of interest to note here that an analogous instance of a cytoplasmic particulate trans-

mission of a fermentative enzyme-forming system has been recently discovered in yeast by Spiegelman *et al.* (61, 62).

ENERGY TRANSPORT AND UTILIZATION

Research on energy transport and its utilization for biosynthetic processes has continued to emphasize the central significance of the group movement concept developed by Lipmann (2, 4, 5).

Phosphate and equivalent groups.—The transphosphorylations between carbohydrate fragments of glycolysis and the adenine system have been under recent study. Meyerhof & Oesper (63) have found the ΔF° of the transfer of the acylphosphate of 1,3-diphosphoglycerate to ADP to be $-4,700$, whereas the analogous reaction involving phosphoenolpyruvate gave a value in the neighborhood of $-4,300$. Bücher (64) has demonstrated that ATP competes with 1,3-diphosphoglycerate rather than with ADP in the forward reaction and suggests that ADP is transferred to the one phosphate of the 1,3-diphosphoglycerate acid on the enzyme surface.

A number of outstanding investigations on the nature of mutase reactions have appeared recently which provide new insight into the mechanisms for the movement of phosphate from one part of a molecule to another. These concepts originated with the research of Leloir and his group (65, 66) indicating that glucose-1,6-diphosphate is the coenzyme for the phosphoglucomutase reaction. They proposed the following novel mechanism to explain its function: glucose-1,6-diphosphate + glucose-1-phosphate \rightleftharpoons glucose-6-phosphate + glucose-1,6-phosphate. In this reaction, the substrate, glucose-1-phosphate, becomes the coenzyme of the next cycle, and the coenzyme is converted into the product, glucose-6-phosphate. Sutherland *et al.* (67) offer supporting evidence [see however (68, 69)] for this mechanism in experiments involving glucose-1-phosphate doubly labeled with P^{32} and C^{14} . A situation and mechanism quite similar to that observed by Leloir and his group was subsequently discovered by Sutherland, Posternak & Cori (70) in the functioning of phosphoglyceric mutase.

A new mechanism of group transfer which promises wide applicability has emerged from the ingenious researches of Doudoroff and his colleagues on the enzyme, sucrose phosphorylase, discovered by Doudoroff, Kaplan & Hassid (71). The phosphorylytic cleavage catalyzed by this enzyme can be reversed to yield sucrose from glucose-1-phosphate and fructose (72). In a series of papers (73 to 78) by the same group, it was demonstrated that this phosphorylase was specific only for the α -D-glucose portion. Further study (79, 80, 81) of this system uncovered another mechanism for the exchange of glycosidic bonds. The discovery started with the observation by Doudoroff *et al.* (79) that incubation of glucose-1-phosphate and radioactive orthophosphate in the presence of sucrose phosphorylase resulted in a rapid equilibration of the isotope between the organic and the inorganic phosphate fractions. The properties of this exchange reaction led to the postulation of the

following reaction: glucose-1-phosphate + enzyme \rightleftharpoons glucose-enzyme + phosphate. The implication of this mechanism is that the glucose-enzyme complex, by preserving the energy of the ester link, should be capable of donating D-glucose to a suitable acceptor. Thus, sucrose phosphorylase can be regarded as a trans-glucosidase capable of exchanging glycosidic and ester bonds and of donating D-glucose to a variety of substrates.

Evidence for the existence of similar enzymes capable of preserving the energy in existent bonds and exchanging glycosidic linkages was available from the earlier studies of polysaccharide synthesizing enzymes (82 to 85). Most recently, this concept has been extended to maltose independently by Doudoroff *et al.* (86), and Monod & Torriani (87, 88). An amyloamylase, isolated from *Escherichia coli*, catalyzes the reversible reaction maltose \rightleftharpoons polysaccharide + glucose. Hehre (89) found an amylsucrase which forms a branched polysaccharide from sucrose.

It is clear from the cases described in the above paragraphs that the intervention of phosphate is apparently not necessary in all cases to preserve the bond energy and transport the desired group to another molecule for the synthesis of a new compound. The use of isotopes has permitted a more detailed understanding of the mechanism underlying the preservation of

(a) (b)

bond energy in such transfer reactions. In principle, cleavage of the C—O—P link of glucose-1-phosphate could occur at either a or b. In an ingenious set of experiments, Cohn (90) analyzed these possibilities during cleavage by phosphorylases and phosphatases. O¹⁸ and P³² were employed to trace the course of events. She found that with the phosphorylases, cleavage occurs at (a), whereas with the phosphatases, the cleavage occurs at (b). The "phosphorylase" type of cleavage would permit the retention of the bond energy between the glucose and the enzyme and thus could account for the trans-glucosidase activity of such enzymes. The "phosphatase" type of cleavage could result in the retention of the energy in the phosphorus residue and enzyme complex. One may, therefore, expect that phosphatases might be capable of transferring phosphate from one compound to another, and indeed, this has been observed by Meyerhof & Green (91, 92), who found that the alkaline phosphatases catalyze a direct transfer of phosphate from glucose-1-phosphate to fructose or glycerol. These findings resemble those reported by Axelrod (93), who termed the enzyme involved "phosphotransferase," although it is apparent from the work of Meyerhof & Green that an ordinary phosphatase is probably involved. The important point to emerge from these researches is that enzymes which we have previously supposed could only waste bond energy by hydrolytic cleavage can be used, under the proper conditions, to preserve the energy of bonds and transfer groups from one molecule to another.

Amino acids, peptides, and proteins.—The problem of amino acid metabolism and interconversion has recently been reviewed critically by Gunsalus (94), one of the outstanding workers in this field. Little can at present be

added to this discussion. A few of the outstanding features may be briefly noted. The primary act of amino acid formation from an organic acid or an amine is not as yet clearly understood. It is, however, clear that not all of the amino acids need be formed by primary synthesis. The existence of a wide variety of transaminases makes it possible to transfer amino groups from one amino acid to some other organic keto acid and thus form a new amino acid. We have, thus another instance of a mechanism in which the energy content of a group can be preserved during transfer. Synthesis of a wide variety of analogous compounds becomes possible without involving for each one the primary biosynthetic act which creates the characteristic group initially.

Insofar as peptide-bond formation is concerned, the evidence is increasingly clear that ATP in some instances supplies the energy for the primary formation of peptide linkage. Johnston & Bloch (95) have demonstrated the necessity of ATP for the synthesis of glutathione from a mixture of cysteine, glutamic acid, and glycine. Speck (96) also presents evidence supporting the role of ATP in primary peptide-bond formation. Once again, however, the pattern emerges of employing existent bonds to make new ones. Again, it is a group of enzymes which had previously been assigned primarily a hydrolytic function which can perform this transfer. There has been increasing support (97, 98, 99) of the earlier observations of Bergmann and his collaborators (100) that peptides can be synthesized via the action of hydrolytic enzymes. Apparently, proteolytic enzymes such as chymotrypsin and trypsin can act as transpeptidases, much as phosphatases can act as phosphate transferring enzymes. Fruton and his collaborators (101) have recently reported the ability of chymotrypsin and papain to catalyze transamidation reactions resulting in the lengthening of peptide chains. These authors, as well as Hanes *et al.* (99), express the view that primary peptide bond formation via an ATP driven reaction may involve relatively few peptide types. The resulting products, although limited in variety, could very easily, by replacement reactions catalyzed by proteolytic enzymes, give rise to a wide variety of different peptides which could then be used for protein synthesis.

One of the primary problems of protein formation is whether they are synthesized via the addition of single amino acids on some pre-existing template or by means of more complex peptide precursors. It is clear of course that if the transpeptidation reaction is of quantitative importance in the synthetic mechanism of the cell, formation of proteins by the serial addition of single amino acids would be a very unlikely mechanism. Evidence against the latter mechanism exists (102, 103).

A most interesting contribution has been made to this problem by Anfinsen & Steinberg (104). They employed the discovery of the possibility of the enzymatic conversion of ovalbumin to plakalbumin by splitting off a hexapeptide. They were able to demonstrate that the incorporation of $C^{14}O_2$ into the aspartic acid residues of the removable hexapeptide was much greater than in the remainder of the protein molecule. The data obtained

would argue against the supposition, therefore, that the ovalbumin molecule as a whole was formed by serial addition of single amino acids and favors the view that peptides or more complex compounds act as intermediates in protein synthesis.

Formation of carbon-carbon bonds.—Knowledge of the energetics and the mechanism of carbon to carbon linkage has expanded considerably in the past few years. The relevant researches have been recently summarized by Lipmann (5) and Ochoa (23). Much of the recent development in this field stemmed from Lipmann's observation (105) of the formation of acetyl phosphate during pyruvate oxidation and his realization that this molecule could in principle act as either a phosphate or an acetate donor. Its action as an energy-rich phosphate transferring device was quickly established (106, 107, 108). Partial confirmation of his other predicted function of acetyl phosphate as an acetate donor came from a study of the reversal of the phosphoroclastic cleavage of pyruvate by Utter, Lipmann & Werkman (109). The curious paradox arose, however, that synthetic acetyl phosphate failed to function in the formation of pyruvate or in the acetylation of choline (110, 111), whereas a combination of its components, acetate, and ATP, was active in both systems. A solution to the paradox began to emerge when Lipmann undertook to study the acetylation of aromatic amines (112). It became apparent that a cofactor was involved in the acetylation reaction. A similar conclusion was arrived at in the study of the formation of acetyl choline (113, 114).

The name coenzyme A was given to this new coenzyme. Subsequent isolation and study of its chemical properties by Lipmann, Novelli, and their co-workers (115, 116, 117) showed that it contained panthothenic acid. The discovery of coenzyme A resolved the paradox of the earlier experiments in which acetyl phosphate appeared to be inactive as an acetylating agent. It appeared that coenzyme A had to intervene as an acetyl carrier and that the active agent was actually acetyl-coenzyme A, a view which has been supported by subsequent work. Stadtman (118) isolated an enzyme, transacetylase, which catalyzes the reversible transfer of the acetyl group of acetyl phosphate to coenzyme A.

Immediately after its discovery, coenzyme A was shown to be a necessary component in the addition of two carbon fragments in a number of acetylation reactions, e.g., in the acetylation of choline (119) and in the synthesis of acetoacetate from acetate and ATP (120). Most recently coenzyme A turned out to be the missing link relating pyruvate metabolism to the tricarboxylic acid cycle. Novelli & Lipmann (121) and Stern & Ochoa (122) demonstrated the synthesis of citrate from acetyl phosphate and oxaloacetate in the presence of coenzyme A and Stadtman's transacetylase. The "condensing" enzyme which carries out the condensation between acetyl-coenzyme A and oxaloacetate to yield citrate and coenzyme A was isolated and purified in Ochoa's laboratory (123). These experiments made possible the next advance by Korkes *et al.* (124), who showed that the oxidative

decarboxylation of pyruvate by coli extracts led, in the presence of trans-acetylase, to the formation of acetyl-coenzyme A. The latter, in the presence of oxaloacetate and the condensing enzyme, yielded citrate. According to these results, then, coenzyme A is the mechanism by which pyruvate enters the Krebs cycle and citrate is the first product.

Thus, again we see the emergence of a mechanism for preserving bond energy in groups and the development of a transfer device which supplies the different biosynthetic mechanisms with both the energy and the group required. The basic unit of carbon chain formation would appear, therefore, to be the two carbon fragments attached as an acetyl group to coenzyme A. These results help to explain the amazing variety of biosynthetic reactions which isotopic experiments indicate involve acetate as a more or less direct and immediate precursor (125, 126). These include everything from the formation of the simple straight chains of fatty acids (127, 128) to the complex branched structures of the steroids.

ENERGETICS OF BIOSYNTHESIS IN THE INTACT CELL

The use of isotopes to trace the pathways of biosynthetic mechanism remains one of the most useful and popular tools for the analysis of intact organisms. The present section will, however, not cover explicitly this type of experiment since some of the pertinent literature has been included in previous sections. A summary will be attempted of some of the more indirect methods for the analysis of the relation of biosynthesis and energy metabolism.

It has been known for some time that agents such as azide, 2,4-dinitrophenol (DNP), and more recently arsenate, are capable of inhibiting a variety of biosynthetic processes without apparently affecting the over-all oxidative processes from which these activities normally derive their energy. Various attempts have been made to understand the mechanism by means of which these agents uncouple the energy generating mechanism from the energy utilizing one.

The mode of action of azide was investigated by Spiegelman, Kamen & Sussman (129). Experiments with P^{32} showed that the presence of azide prevented the entrance of orthophosphorus into the organic fraction. Azide did not however interfere with the coupled oxidation of phosphoglyceraldehyde in the isolated system. These findings and the properties of azide-poisoned fermentation led to the proposal that azide replaced the acylphosphate of 1,3-diphosphoglycerate at the transphosphorylation step. It was presumed that the acylazide so formed spontaneously hydrolyzed into 3-phosphoglycerate and azide. The net result of this reaction would be that no energy-rich phosphate would be available for synthetic activity, although the mechanism permits the generation of the two molecules of ATP required to keep the glycolytic mechanism going. Subsequently, Loomis & Lipmann (130) studied the action of azide on phosphorylation in kidney homogenates, and also came to the conclusion that azide exerts its effect by the destruction

of the energy-rich phosphate bond after its formation and before its transfer to the adenylic system is effected.

Loomis & Lipmann (131) observed that DNP reversibly uncoupled oxidation from phosphorylation in rabbit kidney homogenates. The slow respiratory rate of a phosphate-deficient system was markedly stimulated by DNP, while a phosphate-sufficient system was only slightly stimulated. It appeared as if DNP could replace orthophosphate in this system in a way analogous to the action of arsenate in the coupled oxidation of phosphoglyceraldehyde (132). Teply (39) reinvestigated this system and found that the addition of DNP to preparations of this kind liberated gel-P as ortho-P and is thus equivalent to making inorganic phosphate available. DNP would appear then to act as an "uncoupling" agent at a point subsequent to the actual step of coupled oxidation in a manner analogous to that suggested for azide action (129, 130).

Experiments with inorganic arsenate are perhaps of greater interest since its mode of action as one involving the replacement of phosphate in the oxidation of phosphoglyceraldehyde has been well established by Warburg & Christian (132). Providing no unforeseen complications intervene, the use of arsenate could in principle lead to an experimental answer of the following question: Is phosphate-bond generation the only available source of trapping and utilizing the energy of oxidation? If arsenate could inhibit all observable synthetic activity, and furthermore, if this inhibition could be reversed by its natural metabolic analogue, phosphate, experimental evidence would have been provided for an affirmative answer to the question. Experiments along these lines were performed by Reiner (133) and Sussman & Spiegelman (134). It was shown that arsenate was capable of inhibiting carbohydrate and nitrogen assimilation as well as adaptive enzyme formation in yeast. Furthermore, these inhibitions could be reversed by phosphate. Similar findings were reported by Bonner (135) with growth in *Avena* coleoptile.

Sussman & Spiegelman (134) used the arsenate-phosphate system in an attempt to analyze the relationships amongst the synthetic mechanisms studied. It was reasoned that if all the energy trapping and transport system did flow through the phosphate-generating mechanism, it should be possible to exhibit competitive relations amongst various biosynthetic systems. It was indeed found that the sensitivity of a particular pathway to arsenate was markedly dependent upon whether or not other biosynthetic systems were functioning simultaneously. In addition, the relative sensitivities of the individual biosyntheses to inhibition by arsenate, and to reversal by phosphate, was sufficiently diverse so that suitable adjustments of the proportion of arsenate and phosphate permitted dissociation of synthetic pathways one from the other.

The use of such uncoupling agents provided an opportunity to obtain some information on the general problem of the stability of complex molecules and its relation to cell energetics. It had been established previously

that the process of enzymatic adaptation involves protein modification (136) and that energy was required for its occurrence (137). [For a recent review of the physiology of adaptive enzymes, see (138).] Removal of the adaptive substrate is usually followed by the disappearance of the enzyme system it induces. The question arose whether the adaptive enzyme disappeared under such conditions because the enzyme molecule was inherently unstable in the absence of the adaptive substrate or because the removal of the substrate permits the utilization of the enzyme protein for other synthetic processes going on in the cell. This question was analyzed by Spiegelman & Reiner (139) by examining the effect of inhibitors of synthetic activity on the stability of adaptive enzymes in the absence of substrate. It was found that these enzymes are almost completely stabilized by agents or conditions which prevent synthesis. The conclusion was drawn that the stability of enzymes in the cell was primarily determined by competitive interactions, among synthetic mechanisms. A subsequent investigation by Reiner (133) seemed to indicate that this conclusion could not be generalized with respect to arsenate and the galactose adaptive system, since the latter appeared to disappear in the presence of arsenate. This system was reinvestigated by Sussman & Spiegelman (140), and it was found that the disappearance of the galactozymase in the presence of arsenate was only an apparent one and due primarily to an inhibition by arsenate of galactose fermentation. Arsenate, which does not interfere with maltose metabolism was found to stabilize the maltose adaptive system in the absence of substrate as well as azide.

The finding that the uncoupling of energy generation from utilization leads to stabilization of existent enzyme patterns would appear to contradict the rather widespread assumption that the continued supply of energy is required for the maintenance of complex cellular components. The necessity for an effectively functioning energy generating mechanism for the synthesis as well as breakdown of existent cellular components would be understandable if both processes required the activity of a group transport mechanism. This in turn suggests that enzymes which can catalyze *in vitro* spontaneous breakdown of complex compounds via hydrolytic cleavage (e.g., proteolytic enzymes) do not function in this manner to any considerable extent in the intact cell. Simpson (141) has provided some very suggestive experimental data in support of this thesis in a preliminary report. This author studied the breakdown of protein containing S^{35} -labeled methionine and C^{14} -labeled leucine. It was found that conditions which inhibit energy generation, and therefore biosynthesis, also inhibit the release of the labeled amino acids.

Siegel & Clifton (142) studied oxidative carbohydrate assimilation by *Escherichia coli* during growth. By assuming that the product of glucose assimilation possessed the general form $(CH_2O)_n$, the efficiency could be estimated at 60 per cent. Lactose, with the same free energy per (CH_2O) unit, was assimilated with a smaller efficiency (143).

CONCLUSION

The foregoing survey of energy metabolism and biosynthesis has led to certain general impressions of the present status and future development of the field. It may be of some interest to state some of these explicitly.

Considering only the data which can be interpreted with some precision, there emerges an amazingly consistent picture of the energetic mechanism employed by cells for the synthesis of a variety of compounds ranging widely in their complexity. The primary ways of forming the initial energy containing bonds by reactions coupled to oxidations appear to be relatively limited in number. Variety and flexibility in synthetic capacity are obtained by the involvement of complex group transport mechanisms, which, by preserving the bond energy content, make possible the reshuffling necessary for variety. The basic building units, especially in the formation of carbon skeletons, are very simple ones. As pointed out by Lipmann (5), one is led by these considerations to abandon the older and intuitively more obvious template or cookie-pusher models of synthetic mechanism. In solving the problem of the fabrication of a complex molecule, such as a branched steroid, nature prefers to weave from simple elements rather than stamp them out from more complex precursors. Future research alone can tell us whether this holds for molecules of higher orders of complexity and biological specificity.

One can hardly fail to be impressed with how a few well-thought-out principles have guided a very complex field into fruitful experimentation. Under the circumstances, it is difficult to avoid agreeing with Kluyver's (1) paraphrasing of Hamlet (1), "Enough matter, more art," providing of course that it is the kind of "art" of which men like Kluyver and Lipmann are capable.

Finally a note of caution: one cannot escape the conclusion that regrettably little intense effort is being expended which is aimed at testing the relevancy to the physiology of the intact cell of the various mechanisms for energy generation and utilization which have emerged from enzymological research. The brilliance of the manifold accomplishments which can be recorded in this field should not blind us to the obvious. The only meaningful tests of validity for mechanisms which propose to explain the properties and behavior of cells must come from properly designed experiments with intact, viable, and functioning cells. It is admittedly a matter of extraordinary difficulty to devise definitive experiments which can yield precise answers with the complex living system undisturbed. It is nevertheless a task which must be undertaken with increasing vigor in the ensuing years. Its accomplishment will not be hastened by the present accelerating trend towards the cell homogenizer by workers who are rapidly losing sight of the ultimate reasons for studying the soups and breis which at present hold their attention.

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WATER METABOLISM¹

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TOTAL BODY WATER

There have been some developments in methods for the determination of total body water. The results are usually expressed as a percentage of body weight, i.e. the volume of distribution in litres of some test substance is expressed as a percentage of the body weight in kilograms. As test substances, recognisable isotopic modifications of water have certain theoretical advantages over freely diffusible solutes, since they are less likely to be concentrated within or excluded from particular territories. Pinson & Anderson (1) found that the volume of distribution of water containing tritium in man varied from 57 to 68 per cent of the body weight. Schloerb (2) used deuterium oxide in a more extensive study and found volumes of distribution ranging from 55.9 to 70.2 per cent with a mean of 61.8 per cent for males, and from 45.6 to 59.9 per cent with a mean of 51.9 per cent for females. Since determinations made with the aid of tritium and deuterium compounds are laborious and costly, most workers are perforce content to employ simpler methods. Recently antipyrine has been recommended (3, 4) and although it slowly undergoes metabolism, it is stated to be evenly distributed through the water of human and canine tissues. Friis-Hansen *et al.* (5) have developed a micromethod for the determination of total body water with antipyrine in children. They used it concurrently with deuterium oxide in a number of instances and reported good agreement. These workers found that the percentage of water in the body varied in the usually accepted way with age. Steele *et al.* (6, 7) have also claimed that antipyrine has the same volume of distribution in man as deuterium oxide. Hurst (8), however, has briefly reported simultaneous determinations of total body water with antipyrine and with deuterium oxide in 15 dropsical patients. The volume of distribution of deuterium oxide was on the average 14 per cent greater than that of antipyrine, but in no case had antipyrine reached equilibrium with ascitic fluid or a pleural effusion within 11 hr. This substance may gain in popularity in the future, but there seem still to be some difficulties in its estimation, and the method of Soberman *et al.* (3) requires an ultraviolet spectrophotometer. McCance & Widdowson (9) used urea, and a technique which enabled them to make allowance for the endogenous production of this substance and also for its normal excretion. Levitt & Gaudino (10) have given a useful review of the methods available for determining total body water and its subdivisions and a summary of the results of the various methods as applied to man.

¹ The survey of the literature pertaining to this review was concluded at the end of May, 1951.

INDIVIDUAL SUBCOMPARTMENTS

Evans Blue (T1824) has come to be regarded as the most satisfactory of the dyes to use in determining plasma volume, but a second determination within a short time of the first may colour the subject unpleasantly. The dye has been reported to enter liver cells, but it only leaves the circulation slowly. This is perhaps due to its tendency to combine with plasma albumin [Allen & Orahovats (11)], a fact which may also help to render it nontoxic. It was found to be more toxic than cyanide when tested on liver slices in the absence of albumin. Results agreeing closely with those obtained with T1824 were given by human serum albumin tagged with I^{131} [Crispell *et al.* (12)]. Gregersen *et al.* (13) obtained agreement in dogs between the volumes of distribution of T1824 and a number of antigens which were estimated immunologically. It appears reasonable to believe that this dye measures the true plasma volume. Difficulties may arise, however, when plasma volumes determined in this way are used to calculate whole blood volumes. Thus, McLain *et al.* (14) found discrepancies between the blood volumes of animals determined by exsanguination and by dilution of Evans Blue. These discrepancies were traced to the existence of considerable differences between arterial and whole body haematocrits, caused by variations in the relative proportions of cells and plasma in the blood in different parts of the circulation. Wasserman *et al.* (15) compared blood volumes measured in man with T1824 and with erythrocytes labelled with P^{32} , and also emphasised the importance of the different haematocrit values in different parts of the body. Obvious examples are the high proportion of cells in the blood of the splenic pulp and the increased concentration of cells in the blood in the course of its passage through the kidney.

Apart from such local changes in cell/plasma ratio, it has long been known that the volume of plasma is not constant. Collumbe & Kock (16) recorded changes in plasma volume and thiocyanate space after exercise. Posture is also important, for the total plasma volume may increase by 5 per cent within 1 hr. of changing from the erect to the recumbent posture. Widdowson & McCance (17, 18) have now added the further finding that if a person remains recumbent for three days there is a slow reduction in plasma volume, sometimes to less than the level to which it falls in the same person when he is standing up. On assuming the erect position after three days in bed, the subjects have a further reduction in plasma volume, but it is smaller than usual. The volume of the plasma in edema from various causes requires further investigation (18).

The extracellular fluids fill a number of sub-compartments, each occupied by a continuous fluid phase enclosed within a more or less continuous, if tortuous membrane. They include the plasma and a number of other special collections of fluid. Total extracellular space is measured by the dilution of substances which pass freely through the capillary wall but which it is hoped will not enter cells. Levitt & Gaudino (10) have discussed the various substances which can be used and their peculiar difficulties. There is little doubt

that thiocyanate is the most convenient for many purposes, although they admit that it measures a volume variably intermediate between the extracellular fluid volume and the total body water. There is, of course, no doubt that thiocyanate can pass through some cells, for it is obviously reabsorbed almost completely from the glomerular filtrate—indeed its slow excretion must be numbered among its advantages. It is also known to enter erythrocytes, and an allowance may be made for this in measuring the extracellular fluid volume. A more serious difficulty may arise from its tendency to combine with serum albumin. This, according to Scheinberg & Kowalski (19), may take place to such an extent that the extracellular space determined with thiocyanate is likely to be 30 per cent too low. Entry into cells, on the other hand, would lead to a result which became increasingly too high with the passage of time. The fact that the procedures commonly used give results which cannot be grossly in error suggests that the method is empirically satisfactory when the time allowed for mixing is such that the two principal sources of error neutralise each other. Because of the simplicity, convenience, and wide employment of this technique, further work upon these problems is urgently required.

Inulin has a high enough molecular weight to be free from the suspicion of entering cells. But it also has a low diffusion coefficient and therefore takes a long time to reach equilibrium between blood plasma and the comparatively "dead" spaces which are to be found in the extracellular fluid compartment. As it is rapidly excreted, the only type of equilibrium possible is a dynamic one which can be maintained only by continuous infusion just balancing the rate of excretion. After a single injection, Schachter *et al.* (20) have shown that there is only one moment when the concentration of inulin is the same in the plasma and in the interstitial fluid. The moment would be different for equilibrium between plasma and edema fluids. Various constant infusion techniques have been evolved to allow the attainment of a dynamic equilibrium between plasma and tissues, such as that of Schwartz *et al.* (21). A subsequent modification (22) does away with the need to collect the urine. The usual procedure is based upon the assumption that an intravenous infusion, if given until a steady state is reached, produces equality of inulin concentration in plasma and interstitial fluid. The total amount of inulin in the body may be found by analysing the urine collected from the time of cessation of the infusion until excretion is considered complete, or it may be deduced from the rate of excretion and the rate at which the plasma concentration falls. Schwartz *et al.* (23) showed that inulin and mannitol gave the same volume of distribution in man by these methods, but they are of necessity cumbersome, for it takes something like 6 hr. in man to reach a steady state. Moreover, when the urine has to be collected afterwards, this also takes time. Berne (24) found that even after 8 to 11 hr. in the dog, 3 to 4 per cent of the inulin might not have been excreted. In patients with edema or anasarca, very much longer times would be required for inulin to reach equilibrium, and Berger *et al.* (25) described such a patient who had

excreted only 50 per cent of a dose of inulin in 22 hr. They also mentioned the possibility that inulin was slowly metabolised in their experiments on nephrectomised dogs.

Other substances employed have included radioactive sodium in rats (26) and in rabbits (27). This cannot be fully satisfactory, since sodium is not entirely absent from cells and there are large amounts in bone. Levitt & Gaudino (28), using dogs, measured extracellular fluid with inulin, total body water with deuterium oxide, and body sodium by dilution of Na^{24} . They concluded that 35 m.eq. of cation per litre of intracellular water was sodium, and mentioned the additional difficulties raised by accumulation of sodium in the skeleton. Flexner & Flexner (29) used radioactive sodium in an attempt to measure the extracellular phases of the liver and brain of foetal guinea pigs. They administered Na^{22} to the mother, and then 48 to 72 hr. later removed the foetuses and analysed their heart blood and tissues. Fellers *et al.* (30) studied the thiocyanate and radioactive sodium spaces during human growth from early infancy through adolescence to maturity. Both consistently decreased in proportion to body weight. Incidentally, these workers reported failure to reach equilibrium with inulin and mannitol after 2 hr. Perley *et al.* (31) also determined the volume of distribution of Na^{24} in premature babies, infants, children and adults, and found a variation from 44.8 per cent of the body weight in prematures to 25.2 per cent in adults. Sixteen newborn full-term infants gave an average of 35.2 per cent. They considered that these figures were greater than the actual extracellular space. Wick *et al.* (32) employed glucose labelled with C^{14} in eviscerated rabbits, and found that it had a volume of distribution which remained constant for as long as 3 hr. and was similar to that of thiocyanate.

The intracellular fluid forms the largest subdivision of body water, but it occupies an enormous number of microcompartments, hardly ever in direct continuity, and separated from each other by at least two cell membranes and a layer of extracellular fluid. The intracellular fluid may be likened to the disperse phase of an emulsion, the interstitial fluid being the continuous phase. It follows that fluid cannot be added to or taken away from the intracellular compartment without passing through the extracellular compartment. All exchanges of cell water with the environment must be conducted through the medium of the extracellular fluid. Maintenance of the volume and composition of the intracellular fluids must, therefore, to a considerable extent involve mechanisms such as thirst and renal excretion which operate primarily upon extracellular fluid. It also follows that the volume of intracellular fluids can never be determined directly by a dilution method. It can only be determined by difference, and consequently errors in the methods used to measure total body water and extracellular fluid will lead to inaccuracies in the estimation of the total volume of intracellular water. A recent clinical study by Schwartz *et al.* (33) illustrates some of the difficulties which may crop up during an attempt to follow day-to-day changes in the volume of intracellular fluid.

THE COMPOSITION OF THE BODY

There are many reasons for trying to find out the composition of the body, and attempts have been made to get at it in various ways from time to time. Our knowledge of the chemical composition of foetuses and newborn children has been greatly extended by Widdowson & Spray (34) who have analysed 19 for protein, fat, water, and minerals, and traced the changes in water, fat, minerals, etc., as growth proceeded. Comparable studies of rats, cats, pigs, and mice have also been made (35). A 4-year old child and three adults have been analysed (36). One of the subjects, who had died with a conspicuous clinical edema, was found to have over 80 per cent of water in his body.

It is somewhat surprising that it has only recently been realised how much we can deduce about the composition of the body during life from results of a combination of methods available for determining the volume of the main fluid compartments. Berger *et al.* (25) saw the possibility of determining fat in the living person without recourse to measurements of specific gravity, which can hardly be made on sick patients. McCance & Widdowson (9), with the background of their own detailed analyses, were able to take this much further. They have developed a technique for breaking down the body weight of both normal and abnormal human subjects into cell mass, extracellular fluid, and fat. Their method is likely to be of great clinical utility, for it is easy to carry out, causes little inconvenience to the subject, requires no expensive reagents or esoteric laboratory methods, and is much simpler than methods based upon measurements of specific gravity. It has been applied to normal and obese persons and to undernourished subjects who were undergoing rehabilitation. It showed that recovery was accompanied by a considerable increase of muscular tissue and fat, and a reduction in extracellular fluid even if there had been no clinical edema. These workers were also able to show that the percentage of water in the fat-free part of the body of a normal human being was about 71. This is very near the figure which has been found for other mammals and it must be regarded as one of the great biological constants.

HORMONAL AND NEURAL ADJUSTMENTS

The suprarenals.—Since adrenal hormones directly affect the renal reabsorption of sodium, they may indirectly alter the balance between cellular and extracellular water within the body. They may also directly control the water balance of cells and renal excretion of water. Gaudino & Levitt (37) observed large shifts of water between the cells and extracellular space of dogs treated with desoxycorticosterone acetate. This was a particularly detailed study in which they measured extracellular fluid volume with inulin and total body water with deuterium oxide, and used Na^{24} and K^{42} to trace these cations. Some large movements of water took place in a direction opposite to that to be expected if osmotic pressure had remained the same throughout all compartments. Cole (38, 39) reported changes in composition

of muscle, liver, and testes of rats which followed adrenalectomy and could be reversed by desoxycorticosterone. The total amount of water in the liver was considerably increased after adrenalectomy. Changes have been reported (40) in the osmotic properties of isolated muscles of adrenalectomised frogs, but their significance is not very clear. Another obscure but interesting observation is that of Braun-Menendez (41) who found that desoxycorticosterone acetate increased the fluid intake of rats maintained on a salt-poor diet if they were offered free choice of a number of 0.17 *M* salines to drink, but not if they had plain water.

It has proved easier to study the renal than the extrarenal effects of suprarenal hormones, and the results in this restricted field are clearer. Although desoxycorticosterone promotes sodium retention, it can act as a diuretic, and this action need not involve an increase in glomerular filtration rate (42). It has long been known that water diuresis is not easily induced in patients suffering from Addison's disease. McCance's experiments (43) suggested that this might be accounted for by sodium deficiency leading to dehydration and hypotonicity of the extracellular fluids, but it is becoming clear that adrenal hormones may play a part directly. Møller-Christensen (44) suggested that the suprarenal cortex might play a part in the increased diuretic response which he was able to produce in rats by training them to tolerate increasing doses of water by mouth. Their diuresis became greater and quicker in onset, whilst at the same time the output of sodium chloride was reduced. It is a pity that this short preliminary communication does not yet seem to have been followed up. Boss *et al.* (45) found that untreated adrenalectomised rats had lost their normal diuretic response to a test dose of water. Glomerular filtration rate was reduced, but the minute volume fell more in proportion. Kellogg & Burack (46) found that the diuretic response to water was lost within a few days of adrenalectomy even if the rats were maintained on salt, although the usual diuresis still followed the administration of Ringer's solution. Roemmelt *et al.* (47) suggested that adrenal cortical hormones might promote water diuresis by antagonising the action of the hypophyseal antidiuretic hormone. Even the medullary hormones may play a part, and Horres *et al.* (48) have ascribed this to nor-epinephrine. Some valuable criticisms of work on possible "diuretic" hormones are to be found in a dissertation by Blomhert (49).

Chemically and pharmacologically, some of the sex hormones resemble those of the suprarenal cortex. Zuckerman *et al.* (50) found considerable changes in the percentage of water in the organs of immature female rats treated with estradiol and progesterone. Changes in the water content of the endocrine organs have also been reported in rats treated with testosterone propionate (51). The licorice story sheds light on this aspect of the relation between chemical structure and physiological activity. Molhuysen *et al.* (52) investigated a licorice extract which had been causing edema with salt retention in a number of patients and found that it mimicked the activity of the suprarenal salt-conserving hormones. Then Mehta (53) called atten-

tion to the report (54) that licorice extracts contained a number of active sterols. One of them, glycyrrhetic acid (55), has a formula like those of the group of steroid hormones which includes desoxycorticosterone. The Dutch experiences have been confirmed in America, and one case of Addison's disease seems to have been successfully treated with licorice extract. The formulae of the cardiac glycosides also bear some resemblance to those of the salt-regulating hormones, and Aikawa *et al.* (56) report that intravenous injections of 1.2 mg. of digoxin may cause shifts of body water in people without evidence of cardiovascular disease.

Alterations in the distribution of water occur in some clinical syndromes in which the suprarenals may be involved. No attempt has been made to explore the vast literature of rheumatic diseases which characteristically involve exudation and other disturbances of fluid relations. Reid *et al.* (57), however, have made the novel suggestion that salicylates exert their beneficial action by causing dehydration, primarily of the cells. Following up this suggestion, Copeman & Pugh (58) set out to treat rheumatic fever by drastic dehydration produced by other means, with remarkable success. They even seem to have reproduced many of the familiar side-effects of salicylate medication. Cushing's syndrome has been reported to follow the administration of large doses of aspirin (59), and Kelemen *et al.* (60) observed eosinopenia and histological signs of an "alarm-reaction" after large doses of salicylate. This last observation awaits confirmation (61); but alterations of steroid metabolism pointing to altered adrenal cortical function have been detected (62). Activation of the suprarenal cortex by the hypophyseal adrenocorticotrophic hormone (ACTH) is possibly the mediator of these effects, for ACTH has been shown to have profound effects on rheumatism during the past few years. Interpretation of many observations in this field is difficult because of the almost endless varieties of clinical "rheumatism" and the ubiquity of the "alarm-reaction." Selye (63) has presented evidence that almost any disturbance of the organism calls forth a response from the suprarenals through the release of ACTH. When treatment is drastic, it is hard to disentangle the relative importance of the disease and the therapy as "stressors." The disturbance of water metabolism in pink disease is singularly obscure. It has recently been claimed in Australia that pink disease is a disease of adaptation with manifestations of suprarenal hypofunction (64). The reports were convincing, but this novel view of its pathology has not been accepted wholeheartedly in some places where pink disease is common. This is a problem which chemical pathologists should soon be able to solve.

The hypophysis.—There is no doubt about the association of the hypophysis with water metabolism, and recent work has been concerned mainly with the filling in of detail. The most important paper on the action of the posterior lobe is by O'Connor (65). The author gave a detailed account of the release of the neurohypophyseal antidiuretic hormone in the dog, the amount in the blood in relation to the stimulus (hypertonicity), and the response of

the kidneys. He concluded that the antidiuretic hormone affects only the reabsorption of water and has no true chloruretic effect. Heller (66), in a comparative study on the neurohypophysis, also concluded that neurohypophyseal hormones play no essential part in electrolyte economy. Hare *et al.* (67) compared osmotic diuresis in normal dogs and in dogs with experimental diabetes insipidus, and concluded that the antidiuretic hormone never controlled the reabsorption of more than 15 per cent of the water filtered through the glomeruli. Ralli *et al.* (68) found that pitressin treated with thioglycolate still possessed antidiuretic activity in the rat and suggested that the commercial preparation contained two antidiuretic fractions, one active in rat and dog, the other in the rat only. However, Ames & van Dyke (69) have since found that thioglycolate alone possesses antidiuretic potency when administered to rats by subcutaneous or intraperitoneal injection, and have concluded that there is no unequivocal evidence for more than one antidiuretic fraction in pitressin. Antidiuretic activity has been detected in the blood of the rat (70, 71). Sawyer (72) claimed that the frog water-balance principle is independent of the antidiuretic hormone. It acts by increasing water uptake through the skin and is associated with the oxytocic fraction of pituitary extracts. Sawyer has since published evidence (73) that posterior pituitary extracts may also exert an antidiuretic action in frogs. This activity also is associated with the oxytocic fraction, whereas mammalian antidiuretic hormone is associated with the pressor fraction of commercial extracts. Moreover, the diminution in urine flow in the frog was not brought about by increased reabsorption of water, but by a reduction in glomerular filtration consequent upon constriction of the afferent arterioles. Apart from the possibility that there is more than one pituitary antidiuretic hormone, the origin of antidiuretic substances from sources other than the neurohypophysis has sometimes been suggested. Thus, Croxatto *et al.* (74) have obtained an antidiuretic substance, which may be a peptide, by the prolonged peptic digestion of plasma globulin fractions. It remains to be seen whether this substance acts directly on the tubules. Baez *et al.* (75) reported that ferritin and apoferritin possessed high antidiuretic potency in hydrated dogs and rabbits, but they seem now to have concluded that ferritin is not antidiuretic in its own right (76). It appears to act by releasing the neurohypophyseal antidiuretic hormone. The adenohypophysis may also play a part in water metabolism. It is well known to be necessary for the successful development of experimental diabetes insipidus. Pickford & Watt (77) have observed low inulin and diodone clearances and an impaired diuretic response to water in patients with anterior pituitary lesions. Earle *et al.* (78) also found considerable reduction in glomerular filtration rate, renal plasma flow, and tubular functions (T_{MD} , T_{MG} , T_{MPAH}) in hypophysectomised dogs, together with an impaired diuretic response to water. These animals had atrophic changes in all three layers of the suprarenal cortex, but their serum sodium was normal. Bodo *et al.* (79) added the observations that although a test dose of water was poorly excreted by these

animals, none remained in the stomach after 40 min.; and that the clinical picture of experimental diabetes insipidus could be produced in them by administration of the hypophyseal growth hormone. Water diuresis was largely restored, but improvements in glomerular filtration rate and renal circulation were relatively slight. Administration of the growth hormone to rats has been found to lead to a "pseudo-obesity" due actually to excessive storage of water and protein in the tissues (80).

Neurological factors.—Nerve impulses are generally regarded as mediating the release of antidiuretic hormone from the neurohypophysis. The antidiuretic effects of pain, smoking, and emotion can occur without diminution of the glomerular filtration rate and are probably produced by way of the hypothalamus (81, 82). Indeed, the response to nicotine, administered intravenously or by smoking, has been recommended as a test of supraoptico-hypophyseal function in the diagnosis of diabetes insipidus (83, 84). Kelsall (85) also found no diminution in endogenous creatinine clearance to accompany the antidiuresis induced by ischaemic muscle pain in man. Even rabbits under the influence of emotional stimuli may show antidiuresis without reduction in glomerular filtration rate (86), although filtration rate and minute volume commonly vary in the same sense in this animal (87). An antidiuretic response of the mother animal to suckling has been described in rabbits (88). It can be mimicked by injections of antidiuretic hormone, and probably depends upon release of the endogenous hormone by a reflex from the mammary area—a phenomenon which suggests an interesting parallelism with the "let-down" of milk in the cow. Oliguria has sometimes been noticed after ventriculography, and Weinberg *et al.* (89) have investigated renal function during intracranial air studies. Water diuresis was inhibited, but as the effects observed included albuminuria and sometimes haematuria also, they can hardly be ascribed solely to the release of antidiuretic hormone. Taylor & Noble (90) detected antidiuretic activity in the urine of humans after partial dehydration, spontaneous or induced (venesection) fainting, and electroplexy. Rats with electrolytic lesions near the ventromedian hypothalamic nuclei may pass into a curious state of chronic dehydration in which the serum sodium concentration is raised (91). There seems to be a continuous oversecretion of antidiuretic hormone in response to the chronic hypertonicity, so that diuresis can only be elicited by the second of two doses of water. It has been suggested that alcohol diuresis may be due to an altered sensitivity of the hypothalamo-hypophyseal system (92). In addition, the antidiuretic effect of substituted 3-hydroxycinchoninic acids in the rat has been shown to be abolished by neurohypophysectomy (93). This long and somewhat heterogeneous collection of instances suggests that many stimuli influence water balance through nervous paths converging on the hypothalamic region.

More interesting in some respects are recent hints of a direct nervous control over the function of the renal tubules. Handley & Keller (94), on the basis of renal function tests, were led to suggest that surgical damage to

the anterior hypothalamus in dogs led by a neural mechanism to a reduction in the number of active nephrons. Cook *et al.* (95), using dogs anaesthetised with pentothal, observed that acetylcholine, injected into the abdominal aorta in doses which did not affect the systemic arterial pressure, increased the renal excretion of water: epinephrine diminished it. Atropine blocked the effect of acetylcholine, and dibenamine blocked the effect of epinephrine, but not the similar effect of arterenol. By far the most interesting study is that of Kaplan & Rapoport (96). They recommended the hydropenic dog during osmotic diuresis as a test preparation, because its urine volume is strictly determined by the urinary solute load. After unilateral division of the splanchnic nerve, the dependence of minute volume on the rate of solute excretion remained normal on the denervated side, but both were increased. If the relation of minute volume to solute load was determined by the water-absorbing activity of the distal tubule, it follows that denervation considerably reduced the amount of solute reabsorbed by the proximal tubules, for there was no significant alteration in either renal plasma flow or glomerular filtration rate. Blake (97) claimed that epinephrine may influence the tubular reabsorption of sodium, for he found that the concentration of sodium in the urine of hydropenic dogs was considerably diminished by epinephrine even in the absence of alterations in glomerular filtration rate or minute volume. Also Cort (98) has described the reversible relief of post-traumatic anuria in cats by blocking the splanchnic nerves or by applying procaine to the corresponding paravertebral ganglia. A certain amount of caution is perhaps necessary in the interpretation of experiments such as these in which vasomotor changes may have occurred in the kidney, for it has been shown that changes in renal arterial pressure alone may modify the excretion of water and of solutes independently (99 to 103). Alterations in tubular function brought about by stimulating nerves or by the use of autonomic drugs and local hormones may be secondary to vascular changes within the kidney. These might not always be revealed by the methods commonly used for measuring renal circulation rate. Corson *et al.* (104), for instance, encountered an apparent decrease in renal plasma flow during diuresis induced in dogs by infusing hypertonic solutions of sodium succinate and fumarate. Further investigation revealed that the renal circulation rate was actually increased, but the extraction rate of *p*-aminohippurate was depressed. Chapman & Henschel (105) found no alteration in *p*-aminohippurate clearance during water diuresis in normal men.

Regulation under the stress of osmotic diuresis.—The administration of hypertonic solutions causes rapid renal excretion of water even from dehydrated animals, for the kidney cannot increase the concentration of the urine above certain limits. Rapoport *et al.* (106), working on dehydrated humans, showed that with 11 different loading solutes, the urine volume always bore the same relation to the amount of solute excreted. These authors determined the amount of osmotic work done by the kidneys under "resting" conditions (107), and claimed that the dilution of the urine which occurred

during the subsequent osmotic diuresis was due to the existence of an upper limit to the rate at which the tubules could perform osmotic work (108). The polyuria of diabetes mellitus is a clinical example of such an osmotic diuresis (109). The dehydrated dog was also found to excrete equal amounts of water with equivalent amounts of many different solutes (110). All this points rather strongly to the reabsorption of water *qua* water as an active process, at least in the distal tubule. The conclusion, however, that the fall in the urinary concentration with increasing minute volume is due to an upper limit to tubular osmotic work is almost certainly wrong. Experiments by Dean & McCance (111) on the diuretic response of human infants and adults revealed no evidence whatever of such an upper limit. One of us has calculated the osmotic work performed by the kidneys of the dogs studied by Wesson & Anslow (112) during extreme osmotic diuresis induced with hypertonic solutions of mannitol. The osmotic work was increasing almost in direct proportion to minute volume even when this exceeded half the glomerular filtration rate. Moreover, Rapoport's (108) own published results show that the "biological maximum" of osmotic work was only reached at minute volumes of more than 10 ml. per min. per 1.73 m.², whereas most of the fall in urinary osmolar concentration had occurred at much lower rates of flow.

Brodsky & Rapoport (113) have now studied osmotic diuresis in patients with diabetes insipidus. After being deprived of water for 8 hr., these patients were still producing 4 to 5 ml. per min. of hypotonic urine. The infusion of 25 per cent mannitol raised the minute volume to about three times the former level. The urine osmotic pressure rose [as it may do in infants (111)] instead of falling as it would have done in a normal adult, but it still remained below that of the plasma. After treatment with pitressin, the same patients gave a fairly normal response—a more dramatic diuresis with a fall in the previously high osmotic pressure of the urine. The relation of minute volume to solute load was now normal. Without pitressin the minute volume had always been 5 to 10 ml. above normal for a given solute load. The conclusion that active secretion of water into the tubules may occur in diabetes insipidus hardly seems justified, but there does seem to be a basal production of hypotonic urine which the osmotic diuresis only partly swamps. It seems, however, that such a basal production of dilute urine could as easily be achieved by active reabsorption of solutes as by active excretion of water.

Miscellaneous.—A little more evidence has been presented which bears on Borst's (114) suggestion that renal conservation of water is adjusted to maintain the normal volume of the plasma or extracellular fluid compartment. Wesson *et al.* (115) have devised means of following renal function over long enough periods to allow the volumes of the fluid compartments to reach equilibrium. This work is only just beginning, but already it has revealed that sodium excretion may vary with the volume of the extracellular fluids even when the filtered load does not change. This implies regulation of

tubular activity. Moreover, Raisz *et al.* (116) found that the changes in renal haemodynamics which followed sudden expansion of the extracellular fluid volume in dogs outlasted the general cardiovascular reactions. Orloff & Blake (117) described diuresis in dogs following an increase in the volume of circulating plasma produced by infusion of salt-free human serum albumin. The mechanism of such adjustments remains to be discovered. The convergence upon the hypothalamus of proprioceptive impulses from the vascular bed might be a possibility worth investigating. Hungerland (118) set out to investigate an old suggestion that fluids administered orally and parenterally differed in therapeutic efficacy because in one case they were absorbed through the portal circulation and taken to the liver, whereas in the other case, they were placed directly into the systemic circulation. He administered Ringer's solution and isotonic glucose to normal human infants by both routes and found that the mode of administration made no significant difference to the excretion of water and salt during the subsequent 4 hr.

Important reviews of renal salt and water excretion have been published by Kruhøffer (119) and by Berliner (120). McCance (121) has reviewed the physiology of the kidney in infancy. Since then, Dicker & Heller (122) have described water diuresis in newborn guinea pigs.

THIRST, CASTAWAYS, AND DESERT RODENTS

There have been a few new studies of the osmotic achievements of the kidneys of different species. Human kidneys cannot concentrate sodium chloride as highly as it is already concentrated in sea water. Consequently, modern castaways fare no better on sea water than the Ancient Mariner. Other animals are better equipped to face dehydration, for they require less water to excrete their osmotically active waste products. Desert rodents must be able to withstand drought, and it has been found that the kangaroo rat and pocket mouse could live on dry grain (123). These animals could concentrate sodium in their urine to 908 mM and chloride to 1220 mM, compared with 600 mM for the rat, 370 for the dog, and 320 for man. It is not so surprising that Schmidt-Nielsen's kangaroo rats could thrive with only sea water to drink (124). Ames & van Dyke (125) found antidiuretic activity in all specimens of urine from these animals, and also that although the kangaroo rat's pituitary was five to six times smaller than that of the laboratory rat, it contained more antidiuretic hormone. Albrecht (126) studied toxicity of sea water to rats, mice, guinea pigs, dogs and seals. Seals could not concentrate chloride in their urine more highly than in sea water, and were no more resistant than the other mammals. Ladd & Raisz (127) have emphasised the great ease with which dogs can excrete ingested salt. No tendency to edema was noticed in normal dogs when their dietary salt intake was increased by 4 gm. per kg. per day for a week. There was an initial large increase in glomerular filtration rate and in renal plasma flow, but these returned to normal in a day or so, although the excess salt continued to be excreted satisfactorily. The authors contrast this performance

with that of man, in whom the ingestion of .5 gm. per kg. per day rapidly leads to retention of salt and water.

Holmes & Gregersen (128, 129, 130) have published some interesting studies of the mechanism of thirst in dogs. They confirmed early work showing that intravenous infusion of hypertonic solutions is an excellent method of evoking thirst, but they pointed out that the drinking response, although reproducible in any one animal, showed large individual variations in amount and timing. Many unexplained factors appear to intervene between the osmotic stimulus and the quantitative response. Wolf (131) concluded, after a very complicated discussion, that a major part in the mechanism of thirst is played by osmoreceptors of the kind postulated by Verney. These are conceived as the end organs for the afferent side of a reflex arc mediating thirst. Their adequate stimulus is probably the dehydration of their own cells induced by increases in extracellular osmotic pressure. However, it has now been shown (132, 133) that electrolyte-depleted dogs may develop a chronic syndrome of polydipsia and polyuria, although their cells are probably overhydrated. Why electrolyte depletion should sometimes cause this clinical picture is not clear. Bristol (134) reported that his sodium-depleted dogs showed impaired excretion of a test dose of water (43) and greater susceptibility to water intoxication. These effects could both be explained by diminished extracellular osmotic pressure which would tend to divert the water into cells.

EDEMA

Edema still presents unsolved problems, and a certain amount of new work has been done upon them. It is still being suggested that the abnormal production of some antidiuretic substance may contribute to the development of edema. Gopalan (135) found antidiuretic activity in the urine of patients with nutritional edema in South India. Dicker (136) kept rats on protein-deficient diets until they developed edema, and found antidiuretic activity in their urine. Retention of water unaccompanied by salt is, however, uncommon. Goodyer *et al.* (137) investigated an earlier suggestion that antidiuretic substances played a part in the development of anasarca associated with hepatic cirrhosis. They concluded that increased renal tubular reabsorption of sodium rather than of water was involved. Protein deficiency may also operate to produce edema otherwise than through the kidneys. Muntwyler *et al.* (138) kept rats and dogs on a low-protein regime, and found that although there was an absolute decrease in plasma volume and in thiocyanate space, both were increased relative to actual body weight. Cizek & Zucker (139) also observed an increase in thiocyanate space in dogs when their plasma proteins were depleted by plasmapheresis. McCance (140), in the course of a particularly detailed review of the problem of nutritional edema, has stressed that the fundamental change is an increase in the volume of the extracellular fluid, whether edema is clinically apparent or not. It should perhaps be remarked that the simple explanation that fluid

passes from the blood vessels to the interstitial compartments as a result of low colloid osmotic pressure of the plasma is inadequate, since the amount of edema fluid that accumulates may be grossly in excess of any reduction in the plasma volume. The edema fluid is formed from the plasma, but the volume of this is maintained from the environment by ingestion. In addition to the problem of why edematous patients do not excrete their excess fluid, there is the problem of why they drink it in the first place. It is probably unnecessary to postulate an abnormality of the thirst mechanism as such, however, because excessive renal retention of sodium would cause appropriate quantities of excess water to be ingested through the operation of the normal thirst mechanism.

The edema of congestive heart failure is now generally attributed to excessive reabsorption of sodium by the renal tubules, for it can occur without a diminution in glomerular filtration rate (141). When cardiac edema is being dissipated, the urine has approximately the composition of the edema fluid. This is an example of what Borst (142) has called "saline diuresis." Borst regards this type of diuresis as the normal physiological accompaniment of an increase in cardiac output. The converse process—retention of salt and water when cardiac output declines—is a homeostatic mechanism tending to sustain the circulation by keeping the vessels filled, but when the heart fails it may lead to edema. Some attempts have been made to find an explanation of the periods of "spontaneous" diuresis which characteristically occur from time to time in edematous cardiac patients. Brod & Fejfar (143) suggested that the first event was an increase in renal circulation rate, which initiated diuresis and so caused haemoconcentration. The haemoconcentration was then supposed to withdraw fluid osmotically from the tissues and so keep up the diuresis. These authors observed a fall in the inulin U/P ratio, and seem to have drawn from this the false conclusion that the tubular reabsorption of water was inhibited. In fact, their figures show that the glomerular filtration rate had increased and that the absolute rate of reabsorption of water had increased also. Sirota *et al.* (144) studied spontaneous diurnal variations in renal function in normal humans as a basis for comparing the results on patients with cardiac failure (145). In six patients with persistent edema glomerular filtration rate, minute volume, and sodium excretion all increased during sleep instead of decreasing as they did in the controls. Fishman *et al.* (146) imitated the effects of a pericardial effusion in dogs by enclosing the heart in a cellophane bag. Tamponade developed gradually and the animals survived about a fortnight. Cardiac output was maintained until a couple of days before death. The first detectable change was an increase in venous pressure after two to three days. No change in renal plasma flow occurred for eight days, or in glomerular filtration rate for 11 to 12 days. But from the time that the venous pressure began to rise, sodium excretion fell, and an increase in thiocyanate space was detectable in four to five days. Although the authors speak in terms of an impaired power of the kidneys to excrete sodium chloride, there must, in fact, have

been an active increase in tubular reabsorption, for serum sodium concentration was rising and glomerular filtration rate was undiminished. How the increased venous pressure was connected with the retention of sodium is not clear. Epstein *et al.* (147) found in a study of the antidiuresis of quiet standing that the distribution as well as the composition and total volume of the plasma was a factor in regulating sodium excretion. Jiménez-Díaz (148, 149) has made the novel suggestion that the absence of a renal hormone which regulates capillary permeability is a factor in the development of nephrotic edema; for nephrectomy may lead to a diminution in plasma volume and an increase in the volume of extracellular fluid, both of which can be prevented by injections of kidney extracts.

THE WATER BALANCE OF CELLS AND TISSUES

Osmosis is generally supposed to determine the movement of water between the several compartments in such a way that however much the composition of their fluid contents may vary, their osmotic pressures always remain equal [Peters (150)]. This involves the assumption that the cell membranes are everywhere freely permeable to water, and also the assumption that there is no active transport of water as such to disturb the state of osmotic equilibrium. There have been observations which did not fit in with the classical theory, but it was so simple and so satisfactory for most purposes that the discrepancies tended to be explained away. It was postulated that some intracellular base is bound in an osmotically inactive form. Danowski (151) discussed this matter in a recent review, and suggested that variations in the amount of intracellular base which was thus inactivated might provide a mechanism whereby cell water could be increased or decreased without moving base into or out of the cells. But the amount of base which is bound in this still unexplained manner cannot be determined except by assuming osmotic equilibrium. It follows that this modification has made the original theory insusceptible either of proof or of disproof, even should it become possible to make a satisfactory complete chemical analysis of the intracellular fluids. Additional observations have been made during the past few years which lead to the suggestion that the time may have come to re-examine the classical theory and perhaps to replace it rather than to patch it further.

The extracellular fluid of an animal furnishes a sort of "osmostat" in that it provides all the cells with a common circumambient osmotic pressure. Yet it has been known for more than half a century that different tissues may respond differently to changes in extracellular osmotic pressure; and new observations have been recorded during the period under review. Some effects of hormones on the distribution of body water have already been mentioned. Thus, certain tissues, but not others, in rats treated with steroid hormones by Zuckerman *et al.* (50) showed alterations of up to 5 per cent in water content without change in extracellular osmotic pressure. McCance & Robinson (152) dehydrated rats with hypertonic saline and found that

different tissues lost water to very different extents. Flanagan *et al.* (153) found similar disparities in the uptake of water by different organs of adrenalectomised dogs depleted of extracellular sodium chloride. The tissue water and electrolytes varied independently, so that the changes were not likely to be due simply to alterations in the proportion of extracellular space in the tissues.

Opie (154) reported that if isolated rat tissues were to be prevented from swelling, they had to be placed in distinctly hypertonic solutions. The actual concentrations varied from one tissue to another. Now, if the isolated tissues were only in osmotic equilibrium with these hypertonic solutions, the question arises, "Why did not these same tissues swell in less concentrated surroundings in the body?" The extracellular fluid which is the normal habitat of the tissue cells must be functionally isotonic during life. Opie deduced that the intracellular fluids were maintained in a state of hypertonicity to their immediate surroundings, but seems not to have realised that he had said something rather startling. At any rate, he made no comment on the possible significance of his discovery. Later (155) he found that the hypertonicity of liver and kidney cells was abolished by certain toxic agents, such as chloroform, carbon tetrachloride, and potassium chromate, and further that this effect was reversed on recovery. A recent study by Moon (156) serves as a reminder that cloudy swelling of the renal tubular epithelium is a characteristic post-mortem finding in human cases of poisoning with carbon tetrachloride. This process, too, must be reversed in patients who recover. A more detailed investigation with Rothbard (157) has confirmed Opie's original conclusion that liver and kidney behave as if their cells are osmometers containing fluid whose osmotic pressure is about twice that of the extracellular fluids, whereas fibrous tissues behave more like gels, and corium and muscle show some of the features of each. Opie still refrained from suggesting a mechanism for these surprising osmotic inequalities. It is tempting to suggest that the healthy cells in the body were behaving as if they were in equilibrium with the less concentrated extracellular fluids, because they were then able to draw upon metabolic energy. Elkinton (158), writing in this publication two years ago, made the comment that the findings in Opie's first paper (154) "suggest disparities between tissues of cellular osmotic pressure, disparities that conceivably are present during life and are conditioned by metabolic processes." It is now probably justifiable to go considerably further than this, although Opie's conclusions might be criticised on the grounds that the tissues were isolated but not surviving, and that he used pure sodium chloride solutions instead of balanced saline media.

Active transport of water.—Workers in Krebs' laboratory (159) found, in the course of a study of the assimilation of glutamic acid by slices of a number of guinea pig tissues, that these slices swelled under anaerobic conditions even in a balanced isotonic medium. Increases in weight of up to about 50 per cent were observed in brain, kidney, liver, lung, and spleen.

The authors concluded that energy derived from respiration was an important factor in regulating the fluid balance of the tissues. Aebi (160) set out to discover the optimal ionic composition for a medium to maintain surviving slices of guinea pig liver. Incidentally, he disclosed a relation between the water content and the respiration of the slices. Slices deprived of oxygen were swollen and opaque; and this swelling was reversible when oxygen was supplied. He seems to have inclined to the view that swelling occurred as the result of some defect in the medium and, when it occurred, it interfered with respiration. Allen & Orahovats (11) recently found that rat liver slices poisoned with Evans Blue contained more water when their respiration was depressed.

Robinson (161) published a fairly detailed study of the behaviour of rat kidney slices. These swelled in "isotonic" solutions if their respiration was reduced by chilling in ice, by low oxygen tensions or pH, or by cyanide. The swelling that occurred on poisoning with cyanide was shown to be reversible, for when hydrocyanic acid was distilled out of the medium, the water content of the slices diminished as their oxygen consumption recovered. Swelling of the cells was deduced from the amount of water in the slices with the aid of determinations of the extracellular phase by means of inulin. Respiring slices were found to swell less than nonrespiring ones when subjected to corresponding dilutions of the medium. Slices which had been stagnant in isotonic media appeared to throw out water even into hypotonic media when supplied with oxygen at body temperature. Incidentally, the work of Opie was confirmed with balanced media, for chilled slices swelled unless placed in a medium of almost twice the osmolar concentration of the extracellular fluids.

It was suggested that these findings might be easier to interpret if the idea of an intracellular fluid in true osmotic equilibrium with the extracellular fluids was abandoned. If the intracellular fluid is hypertonic, water must continually diffuse into the cells. The internal hypertonicity could then only be maintained by active transport of water outwards across the cell membrane as fast as it entered. At the same time, the cells would be prevented from swelling, but their normal volume would be maintained as a steady state, and not as a true equilibrium. Such a dynamic equilibrium could only be maintained as long as energy was available. The amount of energy required to maintain the water balance of the slices in this way was calculated and found to be proportional to their oxygen consumption, which was measured independently.

Such a conception of water balance within the body as a steady state is consistent with current ideas of the "dynamic state of body constituents." Attempts to treat a number of other biological "equilibria" as steady states have been reviewed by Bertalanffy (162). So far, only approximate theoretical treatment has proved possible, but it seems not too much to hope that such a picture of the water exchanges between the cells, at least of the parenchymatous organs, and the extracellular fluids could account

for all that the classical theory explained, and for the other observations also. Much further work is clearly required, and indeed the idea of water balance as dynamic, rather than static, may prove stimulating in a number of fields. It goes some way towards explaining the high respiratory metabolism of "resting" cells. They may need energy for maintaining the concentration as well as the ionic composition of their contents, which are separated by permeable membranes from very different external media. Such a mechanism as seems to be required for pumping water out of cells could also subserve transport across cells, granted polarity in the sense that extrusion occurred at one end of the cell whilst inward diffusion was allowed to preponderate elsewhere. Thus, outward transport of water on the side of the renal tubular epithelium away from the lumen could account for reabsorption of water. Cells whose interior was kept hypertonic as suggested above could clearly concentrate fluid in the lumen up to a limit, so that this mechanism could account for the production of hypertonic urine. Nicholson (163) found that a kidney poisoned with cyanide responded with diuresis and could not fabricate anisotonic urine. Mercurial diuretics are generally supposed to act by inhibiting the reabsorption of sodium (164, 165), but it is interesting to note that they have also been found to depress the oxygen consumption of kidney slices (166, 167). Moreover, selective absorption might arise from the diffusion of different solutes with or against the convection streams of water which must traverse the cell membranes if the above view is correct. There is little to add to certain quite old cryoscopic studies as direct evidence of such a process. Some recent (unpublished) measurements have revealed a higher concentration of total base in the cells of respiring kidney slices than in the surrounding medium. This difference in concentration was inhibited by cyanide.

It was suggested (161) that this mechanism might be common to many mammalian cells, but it may be even more widespread. A review by Chambers (168) contained hints that some amphibian tissues and protozoa are not in osmotic equilibrium with their surroundings. There is, moreover, a remarkable formal similarity between Robinson's studies of kidney slices and those of Kitching (169, 170) on protozoa which possess contractile vacuoles. These normally maintain an internal hypertonicity by vacuolar expulsion of water, and swell reversibly if this expulsion is prevented by cyanide. Protozoan material has the advantage that the transport of water across the membrane into the vacuole and its subsequent expulsion from the cell can be directly observed; but its respiration is not so readily measured. Kitching's and other related work is reviewed by Prosser (171). Insects possess a number of peculiar osmotic mechanisms. Ramsay (172) has shown that the production of highly anisotonic rectal fluid by mosquito larvae is associated with a special type of epithelium. Many further examples are discussed in Wigglesworth's book (173). Wigglesworth's own investigation of the way in which respiration is regulated by movement of water in the tracheoles is particularly interesting. Lack of oxygen causes fluid to leave

the tracheoles and enter the cells, thus opening the tracheoles to the air. When oxygen is supplied, the fluid is expelled again and partly closes the tracheoles.

Plants provide examples of vacuolated cells whose vacuolar sap has a higher osmotic pressure than the surrounding fluids. Rosene & Bartlett (174) found that anoxia diminished the capacity of radish root hairs as water absorbing organs. Hackett & Thimann (175) have presented evidence that the uptake of water by potato tissue is an active process which requires aerobic conditions and is inhibited by small concentrations of azide, arsenite, fluoracetate and dinitrophenol. Indoleacetic acid increased the uptake of water. This is a general effect of auxins, and they rather generally increase respiration at the same time. There is a short recent review of the water relations of plant cells by Kramer & Currier (176) and a more complete account in the book by Crafts *et al.* (177). There is also an excellent critical discussion of this problem in Stiles's recent book (178).

It is probably necessary to invoke active transport of water wherever osmotic pressure differences are maintained without an adequate physical or hydrostatic explanation. Transport of solutes also undoubtedly occurs, but it would have to be extremely rapid to account for sustained differences in osmotic pressure unless the permeability of the membranes to water were lower than that to solutes. Active transport of water as such, therefore, appears to be a common occurrence in living systems. Living cells have indeed been evolved in intimate relations with water, and it should not be surprising to find that some, at least, have means of controlling its movement actively. Little is known as yet about the mechanism of such transport.

Mechanism.—The fact that kidney slices poisoned with 2,4-dinitrophenol swelled almost as much as those poisoned with cyanide, although their oxygen uptake was increased (179), suggests that energy derived from oxidation was not used directly but through the medium of high-energy phosphate bonds. It appears that 2,4-dinitrophenol seems to make the energy of respiration unavailable for the esterification of inorganic phosphate to adenosinetriphosphate (ATP) (180, 181). This observation is paralleled by the manner in which 2,4-dinitrophenol interferes with other processes of active transport in isolated kidney tissue. Thus, accumulation of phenol red by isolated tubules of the flounder is prevented, among other things, by anoxia, cyanide, and dinitrophenol (182, 183). The same is true of the accumulation of *p*-aminohippurate by slices of rabbit kidney (184). Presumably all these transport processes have a common dependence upon ATP as an intermediate source of energy. Interesting though this is, it gets us no nearer to understanding how the energy of ATP is used to pump water or other substances. Dixon (185) suggested a mechanism whereby energy from ATP could do osmotic work on a substance which was itself phosphorylated. Ussing (186) outlined some mechanisms which might play a part in transferring ions, and remarked that water exchange is linked to cell metabolism by processes not yet understood. More is known about

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muscle than about any other machine for transforming ATP energy into other forms. Szent-Györgyi (187) pointed out that extended and contracted myosin chains hold different amounts of water of hydration. A contractile protein undergoing a cycle of hydration and dehydration might thus be made to pump water. It is, therefore, of great interest that Szent-Györgyi quoted Lajta (work not yet seen in print) as having found that the kidney contains considerable quantities of a protein with properties similar to those of myosin. Goldacre & Lorch (188) have sought to develop the same idea and to relate folding of polypeptide chains to cytoplasmic streaming, amoeboid movement, and the performance of osmotic work. Such a possibility was envisaged in a review by Monné (189). In view of the suggestions that the "pump" may have moving parts, it is interesting to see that Blowers *et al.* (190) found a general parallelism between factors which prevented active transport of cations across the membrane of human erythrocytes and those which stopped a flickering appearance of the cells when they were observed with the phase contrast microscope. Osterhout (191) showed how the maintenance of local differences in osmotic pressure in cells of *Nitella* could lead to transport of water through the cells from a sucrose solution to pure water. This mechanism does not seem essentially different from that of a model for class demonstrations which was described by Brauner (192) in 1932. Huf *et al.* (193) found that active transport of water and salt by isolated frog skin was inhibited by bromoacetate, and that the inhibition might be reversed by pyruvate and lactate. Sawyer (194) seems to suggest that posterior pituitary extract increases the permeability of the skin to water without calling forth an increase in osmotic work. Arens (195) postulated an "active membrane" in plants, which pumps water by electro-osmosis. The potential difference required was supposed to be derived directly from respiration by oscillation of valencies of the heavy metal prosthetic groups of the cytochrome oxidase system. This would be consistent with the abolition of active transport by inhibition of cytochrome oxidase, but it ought not to require the intervention of ATP. Such a mechanism should not be inhibited by 2,4-dinitrophenol.

MISCELLANEOUS CLINICAL ASPECTS

The clinical implications of this dynamic conception of the water balance between cells and extracellular fluid as a steady state have hardly begun to be worked out. It follows from this theory that changes in extracellular osmotic pressure should completely determine shifts of body water only in the absence of alterations in metabolism. [This remains true even if the theory proves wrong in detail. There can be no doubt that the metabolism of cells does influence their fluid exchanges whether by the mechanism suggested above (161) or in some other way.] When metabolism is disturbed, clinicians should be on the look-out for shifts of body water which may seem paradoxical in the light of ascertainable changes in extracellular osmotic pressure—or for the failure of such shifts to occur when they might be

expected. The cells may not be simply at the osmotic mercy of their surroundings, but may take an active part in regulating their water content. If they do so, this is a function which may well become abnormal in disease.

A few recently reported examples of osmotic disturbances acquire new interest in the light of this conception. Thus, Welt *et al.* (196) described what they called "cellular hyperosmolarity" following electrical convulsion therapy. Water disappeared into cells during the convulsion. This was attributed to the release of lactic acid raising the osmotic pressure of the muscle cells. But lactic acid could presumably diffuse out freely, and if it did so it would not cause water to enter osmotically. An alternative explanation might be that anoxia occurred during the convulsion and this interfered with active expulsion of water from cells, which need not have been solely muscle cells. Curare might have lessened the severity of the anoxia by reducing the demand for oxygen by the muscles, which could account for the much smaller shift of water observed when the convulsions were modified with this drug. Sims *et al.* (197) described a persistently low serum sodium concentration in chronic tuberculosis, without symptoms of sodium deficiency such as might be expected from the abnormally low osmotic pressure of the extracellular fluids. This could be interpreted as the setting up of a new steady state.

Neonatal edema seems in some way to be related to difficult labour with intra-uterine anoxia (198) or to prolonged respiratory distress in the newborn (199). If anoxia hindered active expulsion of water, it should lead to excessive accumulation in cells. When the supply of oxygen was improved, this excess water would be expelled, to become manifest as edema or anasarca. However, Gruenwald & Mayberger (200) stated that anoxia played no part in their experiments on the production of hydrops fetalis in guinea pigs by injecting muscle pulp. Kerpel-Fronius *et al.* (201) found no decrease in the percentage of water in the brain of infants dying of severe dehydration. They also found that the circulation was so much impaired that the cerebral venous blood was unusually deprived of its oxygen, and suggested that the nervous symptoms could be explained by cerebral anoxia. It is interesting to speculate whether cerebral anoxia was also responsible for the brain being relatively so well hydrated. More recently, Kerpel-Fronius *et al.* (202) suggested that anoxia might not be limited to the brain, and that dehydration might kill by so far reducing the circulation that most tissues become anoxic. If this be so, then there is the further possibility that anoxia might aggravate the extracellular dehydration by allowing withdrawal of water into the cells, which would further impair the circulation and establish a vicious cycle.

Steffensen (203) found that the volume of distribution of urea was unusually low in thyrotoxic patients. When the metabolic rate was reduced by treatment with methyl thiouracil, their total body water increased. This could be accounted for if the increased metabolism in thyroid toxæmia was accompanied by faster pumping out of water from the cells. Thyroxine has

long been known to possess a diuretic effect in myxedema. This would be expected if the increase in oxygen consumption caused water to be expelled from cells. The extracellular fluid would be diluted thereby, and water diuresis would be expected to follow.

Seldin & Tarail (204) have made a study of the osmotic disturbances in diabetic acidosis, and there is a considerable amount about water balance in the recent review of the role of sodium in disease by Danowski (151).

This review must close without firm conclusion on many matters of importance. The past two years have been marked by an increasing tendency to think in dynamic and kinetic terms. Familiar conceptions based on more static considerations have been challenged. It might be said that the future is more than usually unpredictable. Water metabolism has become more fluid, more mysterious, and more interesting, and therein lies much hope for future progress.

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THE RESPIRATORY SYSTEM

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The period covered by this review¹ (July, 1950 to June, 1951) was marked by the virtual completion of publication of research initiated during World War II and the beginning of emphasis on new problems associated with renewal of military activities.

A significant achievement has been the publication (41) and increasing use of a standardized set of symbols and definitions in respiratory physiology. Recent advances in basic respiratory research have been brilliantly summarized by Fenn (42) for the mechanics of breathing and by Riley (110) for gas exchange.² In the more controversial field of the regulation of respiration, a symposium on chemoreceptor mechanisms has been published (127), but a wholly satisfactory interpretation of the integration of all the factors regulating respiration has yet to be developed.

MECHANICS OF BREATHING

Lung volume.—Using the hydrogen or helium dilution method for residual capacity, Whitfield, Waterhouse & Arnott have reported physiologic norms for the lung volume subdivisions based on measurements in 64 males and 32 females ranging in age from 10 to 69 years (132). The variability obtained in 27 separate determinations in one trained individual was as great as the variability in paired measurements in 19 individuals. In correlating lung volume subdivisions with body weight, height, chest expansion, and radiologic chest volume, it was found that multiple correlations of all anthropometric data with total lung volume, vital capacity, and inspiratory reserve volume gave coefficients of almost unity (134). The effects of body position on lung volume subdivisions were measured in most of the same subjects (133). In each article, a valuable comparison is made with similar data obtained by others. It is not clear why the authors did not correct their own volume data to body conditions of temperature and moisture. The effects

¹ Publications from east European countries are not included. Further, the authors have elected not to include abstracts, agreeing with previous contributors that such material will eventually become available in a more valuable form.

² The clinical journal which published these seminars is to be commended for bringing to the general medical audience physiologic essays of the highest caliber.

of tobacco smoking on lung volume were also studied (131). Bateman (8) has suggested a graphic method for determining the relationship of observed lung volume subdivisions to normal standards.

In extending his investigations of physiologic dead space and functional residual capacity with the nitrogen-meter single-breath technique, Fowler (47) reports variation in dead-space values from 127 ml. in young adult males to 169 ml. in emphysema patients (averages). A control group of elderly individuals had a slightly lower average than the patients. A most important point was that values at similar degrees of lung inflation were similar for all groups. The same procedure was used in studying the effects of posture. The dead space was significantly smaller when the subject was reclining (46). This change is probably an expression of reduced lung inflation, since functional residual capacity measurements in the same study were reduced by 787 ml. in the supine position. The same experimental method applied to patients before and after pneumonectomy indicated a 17 per cent reduction in dead space volume postoperatively (48). An excellent discussion of problems of uneven pulmonary ventilation and dead space measurement is given by Comroe & Fowler (25) who base the discussion on their clinical applications of the nitrogen meter method.

Further attempts have been made by Peyser, Sass-Kortsak & Verzář (107) to demonstrate that functional residual volume increases in response to the specific stimulus of oxygen lack. Clarification of this hypothesis awaits experiments in which correlative data are obtained on instantaneous flow rates, air and tissue viscance, and the concentrations of oxygen and carbon dioxide in the blood. Binet *et al.* (12) have proposed a method for estimation of the dead space and of the alveolar capacity in the intact rabbit based on dubious assumptions about the steady state of carbon dioxide exchange in the presence of auditory or visual stimuli. Of some clinical interest are reports on diurnal variation of vital capacity measurements [Dissmann (35)], a multiple pneumograph type of respiration recording [Clauser (24)], and a correlation of thoracic circumference with end-expiratory position [Gigon (57)].

Pressure-volume relationships.—Proctor, Hardy & McLean (108) have made a promising approach to the study of pulmonary disease with the use of the pneumotachograph, alveolar pressure measurement, and a consideration of the dynamic and static pressure-volume relationships of the lungs. Woods *et al.* (143) have characterized the diaphragmatic and intercostal contributions to the pneumotachograph pattern of the dog. Intrapleural and intraperitoneal pressures and the respiratory air-flow pattern were studied during pure diaphragmatic and pure intercostal breathing. Intercostal muscle activity was found to initiate inspiration and was followed by an integrated contribution from the diaphragm. Mills (99, 100) measured mouth, endotracheal, and endogastric pressures produced during vital capacity maneuvers and during performance of the Flack physical fitness test. He concluded that the inherent errors and theoretical basis of the Flack test are

such that it gives little indication of respiratory or circulatory competence.

The clinical studies of Rothstein & Strzelczyk (112) have demonstrated the interesting fact that the two lungs may act as a single elastomeric body under the influence of pleural pressure changes. Eleven subjects who had been trained in the technique of "unilateral" breathing were examined by differential bronchspirometry. The distribution of tidal volume into the right and left lungs remained the same whether the patient breathed normally or with a localized segment of the chest. This finding is in agreement with that of other workers (115) who found that respiration carried on by one hemidiaphragm ventilated the contralateral lung as well as a normal co-ordinated respiratory act.

Bronchi—air-flow dynamics.—Sheldon & Otis (119) studied the effect of epinephrine on the air-flow resistance of the bronchial tree, measuring pressure drop by the method of Vuilleumier (130a). Control subjects showed no change in alveolar pressure or vital capacity after epinephrine. Asthmatics fairly uniformly showed improvement in vital capacity, even though bronchial dilation could not always be demonstrated by the alveolar pressure method. The authors postulate that part of the improvement may be due to pulmonary vascular constriction which allows more room for air within the lungs. Proctor, Hardy & McLean (108), also using Vuilleumier's method, found bronchial resistance to air flow to be higher on expiration than on inspiration in several cases of pulmonary disease. Earlier work had indicated that the resistance was the same in both phases of respiration in normal subjects. Tiffeneau & Drutel (129) have developed a method of estimating bronchial diameter which depends upon a measurement of the slope of a spirometric tracing before and after inhalation of adrenergic aerosols. Resistances were interposed in the airway for calibration of the technique. This method was also evaluated by Parmeggiani & Pinerolo de Septis (106) who concluded that it was unsatisfactory. Jeddelloh (73) has discussed the effects of surgical anesthesia on the pattern of the patient's pneumotachograph.

Nisell's effectively illustrated monograph (105) considers in the same experiments the effects of carbon dioxide and oxygen tensions on both the bronchial tree and the pulmonary circulation. The experiments on isolated perfused lungs were interpreted as showing bronchial dilation occurring with low partial pressures of oxygen or high partial pressures of carbon dioxide in the inspired air. The authors found in confirmation of other recent work that pulmonary vascular resistance is increased by high carbon dioxide or low oxygen tensions.

Daly & Schweitzer (30) and Daly & Mount (29) have studied bronchomotor responses resulting from stimulation of the chemoreceptors, baroreceptors, and the cervical vagosympathetic nerves in the cat. The variability of bronchomotor response to the various stimulating maneuvers employed was striking.

Most investigators have employed Jackson's method (71a) of measur-

ing the state of constriction of the bronchioles. The tidal volume produced by an unvarying cycle of intermittent positive pressure is measured, and the assumption is made that any changes in tidal volume reflect changes in bronchial resistance to air flow. Unfortunately, this method does not take into account changes in the viscoelastic properties of the lungs that may occur during an experiment. For example, it has been the experience in the reviewers' laboratory that autonomic reflexes arising in the baroreceptors may shift blood from the systemic to the pulmonary circulation (114) and that such alteration of pulmonary blood volume may change the viscoelastic character of the lungs. Under these circumstances, a change in tidal volume might mistakenly be attributed to alterations in bronchial diameter. Vuilleumier's method, as modified by Otis & Proctor (105a), appears to provide a specific measure of airway resistance and should be very valuable in this type of study.

Morton, Klassen & Curtis (102), through carefully controlled clinical observations, have contributed fundamental information about the innervation of the tracheobronchial tree. Electrical or foreign body stimulation of the trachea and primary bronchi via a bronchoscope was carried out in 30 patients before and after high unilateral vagotomy. The patients were able to localize precisely referred bronchial pain. The pain was referred to the ipsilateral chest wall and was abolished in all but three cases by unilateral vagotomy below the recurrent laryngeal nerve. In the three exceptions, pain was referred to the contralateral cervical region, suggesting a partial contralateral pathway for pain. Cough reflex was completely abolished by ipsilateral vagotomy. No difference in the caliber or movement of the bronchi was visible after operation.

Intrapulmonary mixing.—The reports of Fowler and his associates (25, 47) reinforce the argument that study of intrapulmonary mixing must take into account the precise time-flow relationships of the respiratory cycle. The time-response characteristics of the nitrogen meter and the Silverman or Lilly type of flow meter are most satisfactory for this purpose. Since measurement of ventilation distribution inherently includes the dead space, it is essential to recognize variability in the contribution of the latter; although dead space is known to vary with the degree of lung inflation, factors which affect lung volume (such as apparatus resistance) are neglected by many investigators.

Bateman (9) has attempted to analyze nitrogen clearance curves and dead space calculations on the basis of formulae developed for a single chamber model. In view of Fowler's data, the concept of the lungs as a single chamber is much less attractive than it might otherwise be. In order to behave as a single chamber, all the millions of alveolar units would have to have exactly the same pressure-volume characteristics and all conducting units would have to have exactly the same air-flow resistance. Briscoe, Becklake & Rose (18), using a closed circuit helium method, attribute their results in emphysema patients to uneven ventilation rather than enlarge-

ment of the dead space. A new mixing index is proposed by Wolfe & Carlson (142), who used the nitrogen meter in a closed circuit system. The excellent review by Kety (77) is pertinent to the problem of intrapulmonary mixing as well as to the problem of diffusion at other interphases within the body.

BLOOD-ALVEOLAR GAS RELATIONSHIPS

A summary, including his recent additions to concepts of alveolar gas composition, ventilation-perfusion ratios, and diffusion coefficients for oxygen and carbon dioxide has been presented by Riley (110). Riley & Houston have re-examined, according to recent concepts, data obtained during World War II on alveolar gas composition during acclimatization to high altitude (111).

The carbon dioxide equilibration time between pulmonary capillary blood and alveolar gas has been measured semiquantitatively by Forssander (45). After the inspiration of one to three breaths of carbon dioxide mixtures varying from 4 to 25 per cent carbon dioxide, alveolar gas samples were collected by a specially designed valve; over a wide range of inspired carbon dioxide, the corresponding alveolar sample contained between 6.5 and 7.0 per cent carbon dioxide. It would have been interesting to see the results of a short period of breath holding in the same subjects, since the author appeared to be measuring a value close to the mixed venous carbon dioxide concentration.

Measurements of alveolar-arterial pO_2 differences before and after lipiodol bronchograms in 10 patients revealed no residual effects after 48 hours [Black & Roos (14)]. Ferris, Kriete & Kriete (44) have compared their data on the alveolar-arterial pO_2 difference in man with data in the literature, emphasizing the necessity for taking into account the gas exchange ratio. The components of the elevated alveolar-arterial pO_2 difference in coal miners with lung disease have been analyzed by Motley & Tomashefski (104).

CONTROL OF RESPIRATION

Co-ordinating system.—Dirken & Woldring (34, 141) have re-examined, with excellent techniques, the localization and nature of electrical activity in the respiratory centers of the rabbit medulla. With a highly selective pick-up, they recorded action-potential patterns throughout the respiratory region, with simultaneous recording of intrapleural pressure. The latter type of recording is, in the reviewers' opinion, far more valuable than pneumograph recording. Specific electrical-potential patterns were found to correspond to inspiration, expiration, and central vagal activity. The spatial configuration in which these patterns were located confirmed the separate identity of inspiratory and expiratory centers. A fourth pattern of apparently spontaneous medullary spike potentials described by previous workers was shown to be an artifact.

Breckenridge, Hoff & Smith (17) demonstrated that myanesin, a drug which selectively depresses the reticular facilitatory and inhibitory systems,

produces a reversible abolition of apneustic breathing in the midpontine-sectioned animal. They interpret their results as confirming the fundamentally periodic nature of medullary respiratory activity.

Receptor system.—A symposium on the chemoreceptors and chemoreceptive reactions (127) includes numerous excellent papers. De Castro (33) reported his fundamental observations on directly visualized behavior of the carotid body in response to various stimuli. Definite changes in size of the organ and in local circulation were observed in correlation with changes in chemoreceptor drive. Detailed histologic and developmental studies of the chemoreceptor innervation are also given. Other papers in this symposium concerned circulatory as well as respiratory chemoreceptor reflexes. Heymans has also reviewed the regulation of respiration in a separate publication (70).

Winterstein (140) has repeated experiments on the effects of acid injection and acute hypoxia in the chemoreceptor-denervated cat and has concluded that acid and not carbon dioxide is the primary respiratory stimulus. Grodins & Morgan have compared the ventilatory increments with exercise in intact dogs (101) and in dogs with cord transection at T12 (63). Since ventilation increased linearly with oxygen consumption and there were only insignificant changes in $p\text{CO}_2$ and $[\text{H}^+]$ in the intact animal, the authors postulated an unidentified exercise stimulus which was proportional to the metabolic rate. The transected animals differed primarily in having a smaller increase in ventilation per unit increase in metabolic rate, with a resulting respiratory acidosis. The authors concluded that the changes in $p\text{CO}_2$ and $[\text{H}^+]$ could account for approximately 40 per cent of the ventilatory increase. The idea of an exercise stimulus, humoral in origin, was retained to account for the remaining increase. The authors apparently felt safe in neglecting the possible role of oxygen chemoreceptors, since they made no measurements of arterial oxygen partial-pressure. In view of the increased importance of the oxygen chemoreceptor mechanism in the anesthetized dog (13a) it appears questionable that this factor should be neglected when one is attempting to define the interrelationships of components of the respiratory stimulus.

Hickam *et al.* (71) have examined extensively the respiratory responses of untrained human subjects to moderately severe exercise, adding carbon dioxide or reducing oxygen of the inspired air during the exercise period. The effectiveness of the carbon dioxide stimulus did not appear to be affected by exercise. Administration of cylinder oxygen during exercise caused a sharp and almost instantaneous fall in ventilation rate (56 to 47 l. per min.). This observation demonstrates that the oxygen level in the body may be a significant factor in the hyperpnea of exercise, even in the absence of frank hypoxia.

Suskind *et al.* (125) found a slight reduction of arterial $p\text{O}_2$, an increase of $p\text{CO}_2$, and no significant change of alveolar-arterial $p\text{O}_2$ difference in normal subjects during mild exercise. Aviado *et al.* (4) have made a thorough

study of respiratory and circulatory reflexes in a perfused dog heart-lung preparation. New information is provided on a number of well-known reflexes arising in the pulmonary vasculature. Reverse perfusion experiments with maximum pressures in the pulmonary vein suggested that receptors for the Bezold reflexes were in the pulmonary veins. The same preparation was used to study the pulmonary chemoreceptor responses of antihistaminic drugs (5).

Further evidence in the controversy about the relative importance of central and chemoreflex effects of carbon dioxide is provided by Leusen's observations (87) that a given level of carbon dioxide in the fluid perfusing the isolated carotid bifurcation of the dog had a greater stimulative effect than a similar level of carbon dioxide in the fluid perfusing the cerebral ventricles. Leusen also (86) measured the effects of alterations of pH of the fluid perfusing the ventricles and found that respiratory activity corresponded to the pH and $p\text{CO}_2$ of ventricular fluid, which lagged behind the blood changes when these factors were rapidly altered (85).

Boutourline-Young & Smith (16) have presented data on basal ventilation rates in premature and full term infants. Keeri-Szanto *et al.* (75) have re-emphasized the periodicity of respiration which characterizes the newborn period. This periodicity is abolished by inhalation of high oxygen mixtures, which also augment minute ventilation [Graham *et al.* (62)]. Burkhardt, Eastman & Hale (21) have confirmed the fact that antihistaminic drugs stimulate respiration in dogs and have added the observation that the acute hypoxic hyperventilation response is not impaired by the drugs.

Kerr (76) studied the time relationships of thoracic and diaphragmatic muscle contractions, finding that vagotomy caused poor co-ordination of these muscle groups. The inco-ordination was enhanced by increased respiratory activity. Fernandez & Wyss (43) have extended the characterization of afferent fibers in the vagal inspiratory reflex. Responses to electrical stimulation indicate at least two types of fiber. Chatfield & Sarnoff (23) recorded contralateral phrenic action potentials during electrical stimulation of a phrenic nerve. Although blood gases were not measured, it was apparent that the contralateral phrenic was inactive if the respiratory requirements of the animal were met by unilateral stimulation. If ventilation was deficient because of inadequate stimulation or addition of carbon dioxide to the inspired air, contralateral phrenic activity appeared and could be suppressed by increasing the rate, voltage, or duration of the electrical stimulus. The suppression is at least in part mediated by the vagal proprioceptive reflexes. Rylant (113) has used action potentials to trace the origin and course of phrenic nerve impulses.

Reeve, Nanson & Rundle (109) have observed reflex apnea in man and animals from manipulation of upper abdominal viscera and diaphragm. Kruta *et al.* (82) obtained similar results from electrical stimulation of cut splanchnic nerves in patients operated on for hypertension. Jacot (72) has determined factors which modify Head's expiratory reflex.

PULMONARY CIRCULATION

In the isolated perfused cat lung, Duke (38) has demonstrated that 5 to 10 per cent carbon dioxide and oxygen concentrations of less than 15 per cent caused pulmonary vasoconstriction. Sjöstrand (122), by measuring pulmonary gas volumes, demonstrated a shift of blood to the pulmonary circulation when normal man changes from the standing to the recumbent posture. Doyle and co-workers (36) measured pulmonary vascular pressures and blood volumes in 12 subjects during the intravenous infusion of saline. Average pulmonary arterial pressure rose from 12 mm. Hg to 20 mm. Hg with a rise in pulmonary end-artery pressure of 5 to 11 mm. Hg. The pressure increases were accompanied by an increase in the pulmonary and systemic blood volumes. Lagrange & Scheecqmans (83) studied the production of pulmonary edema in small animals by vagotomy and by intracarotid injections of saline and methyl violet. A basis for quantitation of lung edema, based on analysis of protein fractions in the guinea pig lung, has been provided by Hemingway & Campbell (68). Whitteridge (136) has reviewed thoroughly the association of rapid shallow breathing and multiple pulmonary embolism, relating these phenomena to existing knowledge of pulmonary efferent and afferent nervous pathways.

ARTIFICIAL RESPIRATION

The principal development in this field of applied physiology was the demonstration on a large scale of what had been incompletely recognized before, that other methods of manual artificial respiration are more effective than the Schäfer maneuver. In a large number of patients tested shortly after death and in a series of medical students curarized to a state of apnea, Gordon and his co-workers (60, 61) compared several manual methods in terms of pulmonary ventilation produced. They found the Schäfer method often inadequate; among the most satisfactory methods were the Holger Nielsen and the hip-lift, back-pressure methods.

A procedure has been developed by Asmussen & Nielsen (3) for the comparison of manual artificial respiration methods on conscious subjects. The method takes advantage of the balance of elastic forces in the thorax and circumvents many of the objections to the use of normal subjects for such studies. Their investigations showed tidal volumes with the Holger Nielsen method to be more than twice as great as with the Schäfer method.

A large series of dogs were drowned in fresh water by Fainer, Martin & Ivy (40), who presented additional evidence that aspirated water is absorbed by the pulmonary circulation. The authors were unable to demonstrate a difference in recovery rates in animals given artificial respiration by a manual method or by a positive and negative pressure type resuscitator. They point out that ventricular fibrillation is probably the cause of death in fresh water drowning of dogs, and that therefore the fate of their animals was probably not greatly affected by the resuscitation method used. Swann & Spafford (126) have also made a thorough study of the physiologic effects

of fresh- and sea-water drowning. Brucer & Swann (19) have determined the minimal ventilation requirements for resuscitation of dogs following pure nitrogen breathing. Binet & Strumza (13) performed resuscitation in 2,500 experimental animals employing epinephrine, procaine, cardiac massage, and electrical defibrillation of the heart. They conclude that resuscitation is uniformly possible if artificial respiration and cardiac massage are begun within $2\frac{1}{2}$ min. after cardiac arrest occurs. Handford & Ricchiuti (67) concluded from experiments on dogs that unwarranted emphasis has been placed on the possible deleterious effects of the negative airway pressure phase characteristic of positive-negative type resuscitators.

Kowarschik (79) and Knodt (78) have applied large metallic electrodes to various areas on the circumference of the chest, electrically stimulating the underlying muscles to assist respiration in asthmatic patients and in patients with partial respiratory paralysis. Further reports have appeared on the use of rhythmic electrical stimulation of the phrenic nerve for the production of artificial respiration in animals and man (93, 116, 117). The method offers a distinct advantage over pressure breathing because of its salutary effect on the circulation; whether it is feasible for general use remains to be demonstrated. Cross & Roberts (27) have used phrenic nerve excitation in the treatment of asphyxia neonatorum with what they believe are good results. The physiologic principles underlying the treatment of various types of respiratory failure have been reviewed (135).

AVIATION AND SUBMARINE MEDICINE

In past years, interest in this field has been directed chiefly at the respiratory and circulatory effects of pressure breathing and of various degrees of hypoxia. Because of recent developments in the field of aviation, attention has shifted toward the study of explosive decompression and "complete" anoxia.

Explosive decompression.—Gelfan, Nims & Livingston (54) found that rats survived explosive decompression to simulated altitudes of 75,000 ft. but quickly died from anoxic anoxia unless rapidly recompressed. Complete anoxia occurs at 52,000 ft., since the total pressure in the lungs at this altitude is accounted for by the combined partial pressures of water vapor and carbon dioxide. Nonsurviving animals showed edema, congestion, and atelectasis of the lungs. A similar study on monkeys (53) showed that the animals were in general able to survive the mechanical effects of sudden gas expansion in the body cavities if fatal anoxia were prevented. Subjects were explosively decompressed to the 55,000-foot level by Luft, Clamann & Opitz (91) who found that unconsciousness eventually occurs if exposure to that altitude exceeds 6 sec. The authors discuss the reason for the 15 to 17 sec. latent period which precedes unconsciousness.

Burkhardt *et al.* (22) found that there was no difference in mechanical lung injury in guinea pigs explosively decompressed in warm and cold environments. The increased tolerance to explosive decompression in a cold

environment reported by other workers was more probably related to anoxia than to mechanical injury. Haber (64) has examined the effect of water vapor on gas pressure measurements made during decompression. Whittingham (137) has discussed the commercial aviation aspects of explosive decompression.

Decompression sickness.—Margaria & Sendroy (96) suggest that a 5 per cent carbon dioxide in oxygen mixture may diminish the incidence of decompression sickness in divers and aviators, basing their recommendation on the finding that inhalation of such a mixture during the first 30 min. of denitrogenation increased by 20 per cent the amount of nitrogen given off as compared with the amount given off during pure oxygen inhalation. Davison & Haymaker (32), after a clinicopathologic study of five fatalities occurring during decompression chamber training flights, concluded that all of the deaths were due to aeroembolism. Frisoli & Cassen (50) have studied the genesis of rib markings on the lungs of rats following air blast injury, and contrary to the experience of some investigators, found that the lesions corresponded to the ribs rather than the interspaces.

Anoxia.—The effect on ascorbic acid metabolism of repeated exposures of normal subjects to simulated altitude was examined by Krasno *et al.* (81). Their evidence indicates that ascorbic acid depletion may occur as the result of increased utilization, and they suggest dietary regulation to avoid deficiency in personnel exposed to high altitudes. Craven, Chinn & MacVicar (26), by carefully controlling their experiments, were able to show that a carrot diet does not contain a specific factor increasing altitude tolerance in rats, as had been reported by other workers. The carrot diet was demonstrated to produce weight loss, and inanition produced with another diet was equally effective in increasing altitude tolerance. Bell & Northup (10) noted slight but significant adaptation to histotoxic anoxia in rabbits following the daily administration of potassium cyanide.

Hall & Hall (66) found that the time of useful consciousness was doubled while breathing air at 30,000 ft. if carbon dioxide were added to the inspired gas. They attribute this effect to an increase in alveolar pO_2 resulting from increased hyperventilation. Analeptics were found by Adler *et al.* (2) to prevent deterioration of performance when man is exposed to altitude without oxygen. Using a battery of psychologic tests on normal subjects, Dugal & Fiset (37) found that the functions of the higher centers, especially the learning processes, are adversely affected by hypoxia at altitudes as low as 10,000 ft. Gerathewol (56) has developed an electric complex reactor test for the analysis of psychomotor performance under hypoxia. Acclimatization of man to life in the Andes is discussed by Verzár (130).

A comparative study of the altitude tolerance on one animal species from each of the five vertebrate classes was done by Metz (98). The poikilotherms were approximately three times as resistant to anoxia as the homoiotherms, presumably because of the lower brain metabolic rate of the former group. Lipin & Whitehorn (89), and Wilhelm, Comess & Marbarger (138) studied

acclimatization of rats and mice to altitude. Margolis *et al.* (97) examined the effects of paired groups of antagonistic drugs on altitude tolerance. Kramer & Timmons (80) have developed a photoelectric hypoxia warning device employing an earpiece detector. Giulio (58) measured the effects of a fixed resistance on the ventilation pattern at different altitudes.

Pressure breathing.—The extent and significance of reduction of blood volume during increased airway pressure have been studied by Henry (69). He demonstrated that during pressure breathing in a warm environment, the decrease of blood volume may be twice as great as in a cool environment for two reasons: (a) pooling of blood in the venous system is increased in a warm environment because of venodilation, and (b) hemoconcentration is increased in a warm environment because of greater fluid loss in the capillaries. He concludes that since 60 mm. Hg. pressure breathing may cause loss of blood volume in excess of 1,000 cc., the frequency of syncope resulting from this depletion of blood volume would be too great to make this level of pressure breathing practical.

A demonstration (95) was made of the fact that negative pressure applied around the body by the Drinker type respirator is the physiologic and mechanical equivalent of positive pressure breathing given in the usual manner.

Intermittent positive pressure breathing used in resuscitation in both animals and man may have a profoundly deleterious effect on arterial pressure and cardiac output (93, 116). This adverse effect of pressure breathing occurred whenever the circulatory status of the individual was compromised by hemorrhagic shock, barbiturate poisoning, or loss of vasomotor tone due to drugs or central circulatory failure. The therapeutic uses of pressure breathing have been reviewed (92).

METHODS

Loomis & Beyer (90) describe a carbon dioxide and anesthetic gas concentration meter based on absorption of infrared radiation. Jimenez-Vargas (74) has devised a double spirometer with valves controlled by the subject's respiratory movements in such a way that a level record is written and a gas of constant composition may be inspired. Hadorn (65) has used a venturi tube adaptation to record pulmonary ventilation rates and maximum flow rates. Other workers (94) have developed a direct-reading ventilation meter which also employs a modified venturi tube.

Edwards & Miya (39) developed a simple apparatus for giving alternating positive and negative pressure respiration to small animals. The pneumatic balance resuscitator has been used as a respiratory pump in dogs (31). Adams, Ellis & Kaye (1) have designed a pump to imitate the air-flow pattern of normal human respiration. Severinghaus (118) has developed an all-electronic apparatus for phrenic nerve stimulation. A modification of the Gaddum type of respiration recorder for small animals has been described (55). There is also a small animal recording plethysmograph (7).

MISCELLANEOUS

The rise in cerebrospinal fluid pressure when body levels of carbon dioxide are increased was investigated by Goldensohn *et al.* (59). The rise in cerebrospinal fluid pressure during "diffusion respiration" was almost as great as when equal carbon dioxide concentrations were reached by inhalation of carbon dioxide. It was concluded that respiratory movements did not account for the rise in pressure. Shires & Eyer (120) reported measurements of cardiac output and intracardiac pressures during "diffusion respiration."

An extremely sensitive method of carbon monoxide analysis, capable of accuracy in the range below 0.1 per cent hemoglobin saturation, has been developed by Sjösteen & Sjöstrand (121). On the basis of analyses of expired air for minute amounts of carbon monoxide, Sjöstrand (123) believes that carbon monoxide is formed in small quantities in the blood.

Lindskog (88) has reviewed knowledge about collateral respiration. Gaensler *et al.* (52) have made an interesting study of psychologic and other factors in breath-holding ability, with results that should go a long way to discourage the use of this maneuver as a test of fitness or of lung function. Gaensler (51) has also developed a useful index for combining the results of ventilation and static lung volume measurements. Wilson *et al.* (139) have compared the voluntary hyperventilation ability of patients with heart and lung disease. Taylor & Roos (128) have added another to the reports of severe respiratory acidosis in patients undergoing thoracic surgery. Bunker *et al.* (20) have continued their series on the metabolic effects of anesthesia with a report on the effects of ether and cyclopropane in man and in the dog. Curry & Ashburn (28) have summarized lung function measurements which are useful to the surgeon.

Berger & Davenport (11) prepared for the Bureau of Mines a report on present knowledge of the physiologic effects of oxygen and its practical uses in therapy, resuscitation, and rescue work. Bloxson (15) has designed for use in newborn babies a chamber in which slow changes of barometric pressure are used to simulate maternal uterine contractions. The relationship between the physical effects of these pressure changes and the reported physiologic benefits is not readily apparent.

Freyburger *et al.* (49) found that the tetraethylammonium ion in some animal species blocks the pressor response to asphyxia. Morton (103) has described spirometric and pneumographic patterns obtained in patients during surgical anesthesia. Landen & Dortmann (84) have discussed the relative uses of spirometry and blood-gas analysis in clinical lung-function measurements. Balogh (6) has emphasized the error which may occur in oxygen consumption measurements when the barometric pressure is changing rapidly. Stein & Sonnenschein (124) have studied hyperoxic convulsions in cats.

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COMPARATIVE PHYSIOLOGY OF INVERTEBRATE MUSCLE¹

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It is the aim of this review to cover the literature which appeared during the last five years and falls under the scope of the above heading. In addition, some older work will be quoted, either because of its importance with regard to the subject discussed, or because it had not been adequately reviewed elsewhere. This task has been considerably lightened by the appearance of Prosser's *Comparative Animal Physiology* (70) which greatly aided the compilation of material.

As in several other cases in comparative physiology, the great amount of data collected on vertebrates in the field of muscle physiology has tended to lead investigators to transfer, without proof, characteristics of vertebrate muscle to the muscles of invertebrates. Some investigators, like von Uexküll (93) and Jordan (47), have taken a consistent stand against this tendency but an impartial observer will have to admit that their ideas were too vague to show much more than the fact that considerable differences were present. Only recently have the mechanisms of muscular contraction of a few invertebrates been studied with enough precision to illustrate how these invertebrate muscles differ from vertebrate. It should be pointed out that even now there are those who support, at least to a considerable extent, the type of statement made in 1928 by Ritchie (75):

On present evidence there is no need to postulate any mechanism other than that underlying the simple twitch. Different muscles differ profoundly in the speed of the process but not apparently in the kind of process.

However, even in vertebrate muscle there are now known exceptions to the rule of the "simple twitch" being the only mechanism involved, as shown by Kuffler & Gerard (53) in the small nerve fiber-muscle system in the frog. The twitch as present in the vertebrates may well be a specialization which might even be unique for the vertebrates as such.

Whereas striated muscles from vertebrates form a fairly homogenous group with relatively little variation in properties from one to another, in invertebrates much greater differences are present even among the muscles of one animal. Illustrations of this last statement may be found in the muscles of the sea anemones and those of the arthropods. In such case, the muscle chosen as the basis for comparison is of great importance as a poor choice may lead to confusion. For the same reason, investigators may have diffi-

¹ The survey of the literature pertaining to this review was concluded in May, 1951.

culty in understanding each other and may come to quite different conclusions from material that, at first glance, might seem quite similar. In this respect, not only functional but also anatomical factors, such as, whether the muscle fibers run for the whole length of the muscle, or are very short and make up a "muscular field" [Batham & Pantin (10)], should be taken in to consideration. It would seem to this reviewer that at the present time the facts are still too sparse to allow, except in one or two instances, even a tentative classification of muscles according to their properties.

BIOCHEMISTRY OF INVERTEBRATE MUSCLE

In this review it is not intended to more than outline recent advances and research in the field of comparative biochemistry of invertebrate muscle. It is, however, of interest to note that on the one hand considerable similarities to, and on the other hand differences with, the biochemistry of vertebrate muscle have been reported.

With regard to the contractile substance, Hall and collaborators (35) have found that the myosin filaments go through the cross striations in all striated muscles; in invertebrates this holds true for lobster, insect, and pelecypod adductor muscles. In molluscs they report the presence of an additional myosin, paramyosin, which is present in varying amounts in different muscles and may represent more than half of the total amount of myosin present (*Mytilus* adductor muscle). Lajtha (55) finds in muscles of *Mytilus* and other pelecypods the same contractile mechanism as in vertebrates; myosin, actin, and adenosinetriphosphate (ATP) are all present, the latter often in smaller quantities than in vertebrates. He confirms the presence of paramyosin. Calabay (22) prepared ATP from insect muscle using the hind limb and thorax musculature of a locust and found that, in all respects it tested identical with that of the rabbit. Humphrey (41) prepared myosin from a number of fishes, the crab (*Maia squinado*), the clam (*Mya arenaria*) and the oyster (*Saxostrea commercialis*). In all cases he found apyrase activity present, but in different amounts. In a more detailed study on the two types of muscle fibers of the adductor of the oyster (42), he showed that the nacreous (tonic) part contained about half as much adenylic acid and ATP as did the vitreous part. He also found that the apyrase activity was present in two fractions, one in complex with myosin, the other in water-soluble form [see also Gilmour (33) for insect muscle]. Whereas the former needs sulfhydryl groups for proper functioning, the latter is independent of thiol linkages. Chin (25) reports a very high temperature coefficient for the apyrase of the cockroach. Between 5 and 50°C, the Q_{10} was between three and four.

The presence of arginine phosphate instead of creatine phosphate in the muscles of several phyla is well known. Recently it has been shown that in annelids other phosphagens occur. Baldwin & Yudkin (5, 6) first found that one of the two phosphagens differed from arginine phosphate. Subsequently Yudkin (115) showed that the other phosphagen differed from creatine phosphate. Baldwin & Yudkin (6) have also shown that in echinoderms both

creatine and arginine phosphate occur. They consider these findings to show that the phylogenetic line of the vertebrates is more likely to be by way of echinoderms-hemichordates-chordates, than by way of the annelids. However, biochemical relations may be doubtful grounds for establishing relationships, as shown by such findings as those of Dubuisson & Roubert (27), who compared the electrophoretic spectra of muscle protein extracts from the rabbit, the frog, and the snail *Murex*. They found the spectra of the frog and snail to be very similar, but different from that of the rabbit.

Godeaux (34) has investigated the Lundsgaard effect in invertebrate muscle and found it present in all the cases which he investigated (echinoderms—*Cucumaria* body wall and pharynx retractors; annelids—longitudinal muscles of *Hirudo* and *Arenicola*; molluscs—*Venus*, *Tapes*, *Ocenebra*, *Nassa*, *Buccinum*; insects—*Dystiscus*, *Oryctes*; tunicates—*Ciona*). The effect could be obtained by different substances which block sulfhydryl groups either alone or in combination. Harting (36) found that administration of iodoacetate or acetamide gave an increased oxygen uptake in the fast part of the adductor of the scallop, whereas in *Thyone* (echinoderm) muscle it had the expected inhibitory effect.

Humphrey has made a study of muscle enzyme systems. He reports the presence of a very active succinic oxidase system in muscle homogenates from the oyster (39, 40). In the adductor muscle he found that both the nacreous and vitreous parts produced pyruvic as well as lactic acid. The slow part has a lower glycolytic activity due to a lesser ability of converting glucose-6-phosphate into fructose phosphates (44).

In the cockroach, Barron & Tahmisian (7) found a marked sex difference in the oxygen uptake of the muscles, muscles of males consuming about twice as much as those of females. In this animal, Humphrey (43) finds that glycolysis produces both lactic and pyruvic acids. In the grasshopper, glycolysis is greater upon the addition of magnesium and ATP, but is unaffected by iodoacetic acid (45).

The inorganic salt content of molluscan muscle was studied by Hayes & Polluet (37), who came to the conclusion that in marine pelecypods and cephalopods, potassium is the only intrafibrillar ion, whereas in gastropods, calcium, magnesium, and sodium are also present in small quantities. In the fresh water mussel, *Anodonta*, the amount of potassium is only about one seventh of that in marine pelecypods, but the other ions are present in small quantities. Tobias (90) studied the inorganic salt content of hemolymph and muscle of the silkworm. Whereas the small amount of sodium present in the blood of the larvae disappears completely upon pupation, the sodium and potassium content of the muscles remains the same and is very similar to that in other insects and in man.

RELATION BETWEEN NERVE AND MUSCLE

Neuro-humors.—A good deal of attention has been paid to the existence of neuro-humors in the different phyla. For a detailed account of this work, reference may be made to the review by Bacq (2). Lately, this type of ap-

proach has attracted few investigators. As pointed out by Prosser (70), the best evidence for cholinergic transmission has been obtained in the annelids and sipunculids. On the other hand, coelenterates seem to be excluded from having any such mechanism, since, in some of them, even esterase is absent. In other forms, some nerves may be cholinergic, others not, as in the arthropods in which body musculature shows no evidence of any sensitivity to either acetylcholine or esterase poisons but in which good evidence is present for cholinergic control of the heart beat. Nevertheless, Walop & Boot (95) found an esterase present in the muscles of the crab, *Carcinus*. Its concentration was less than that of the presumably true cholinesterase, which they demonstrated in the central nervous system. According to Kooistra (52), the insect (cockroach) gut would be sensitive to acetylcholine although only when it is in hypodynamic condition, from which it is restored by the drug. He also found an esterase present which hydrolyzed mecholyl considerably faster (2.5 times) than acetylcholine. Seaman (84) is of the opinion that esterase activity is necessary for the movements of cilia in protozoa, clams, and frog esophagus.

Adrenergic nerves have been reported for invertebrates but only in relation to intestinal muscle (57, 58). In cephalopod intestines there are indications of tyraminic fibers (92).

Function and number of efferent nerve fibers.—In vertebrates, the striated muscle is divided into a considerable number of motor units, each innervated by one motor fiber. It is generally considered that other efferent fibers, if they are present, do not have a major function in contraction or relaxation. In all invertebrates it will have to be considered that nerve fibers with different functions may be present. In arthropods, such fibers have been isolated and, at least in the molluscs, their existence also seems certain (100). Prosser & Young (72) and Young (114) have shown that stimulation of the giant fiber running to the mantle of the squid results in a quick twitch, and stimulation of the remaining smaller fibers causes a less vigorous contraction in the same part of the mantle. Benson *et al.* (11) found it possible to stimulate two nerve branches to the slow part of the adductor muscle of *Pecten*. Stimulation of one resulted in contraction, whereas the other caused relaxation. The work of Winton (110) and Singh & Singh (85) showed that on application of a direct current to the anterior byssus retractor of *Mytilus*, a contraction of long duration occurs. This contraction can be suppressed by faradic stimulation of the muscle. Such faradic stimulation by itself gives a contraction of comparable magnitude but of short duration. Van Nieuwenhoven (61) working with this preparation found that the direct current contraction can be abolished by ganglionic stimulation with weak alternating current, but that on strong stimulation of the pedal ganglion, a contraction of long duration occurs. Again, this contraction is inhibitable by weak stimulation of the ganglion or, for that matter, by faradic stimulation of the muscle itself. He concludes that two nervous factors are present, one resulting in contraction, the other in relaxation. Pumphrey (73) found

that the anterior adductor muscle of the clam *Mya* receives two types of nerve fibers and that activity in one type is present during fast contractions, whereas the other type shows activity during tonic contraction. The presence of two types of nerve fibers is also well proven in the case of the gut of annelids [Millott 57, 58]. Here, however, ganglion cells are certainly present [Ambache *et al.* (1)] and the effect of the fibers is most likely, therefore, a regulatory one in speeding up or slowing down the neurogenic rhythm.

A similar process may occur in cases where peripheral ganglion cells are present in the somatic musculature, as is likely for the foot of the snail, *Helix*, in which two types of results from stimulation of the pedal ganglion have also been reported (48).

In arthropods the occurrence of different fiber types is well established and it is certain that no ganglion cells are present in the periphery. In the decapod crustaceans, efferent fibers are either motor or inhibitory. A muscle may receive one or more of each kind, in which case they again differ in function. Thus, if two motor fibers innervate a muscle, a considerable qualitative difference between the effects of stimulation is present. Again, when there are more than two motor fibers, each gives a contraction type with its own characteristic. When two inhibitors supply a muscle, one differs from the other in efficiency (105).

Whereas we find a wide divergence in the type of fiber innervating the muscles, the number of fibers is very restricted, only one of each type going to any one muscle. There are indications that in other invertebrate phyla, a small number of fibers may form the innervation of whole muscles. For the columella muscle of the snail, Ramsay (74) reports innervation by relatively few fibers, which are divided in two groups, thick and thin. A single nerve fiber may innervate a large part of the body musculature as shown for the annelid, *Branchiomma vesiculosum*, by Nicol (60). This animal has two giant fibers in the central nervous system which give off direct motor branches to the longitudinal muscles in each segment. In effect, these would be motor fibers, although comparable giant fibers in other animals are entirely intracentral. The fibers were stimulated by electrodes placed on the skin. Single stimuli caused single twitches and the tetanic contraction height was not noticeably larger than that of the single twitch. In this respect, this system behaves like that of the giant motor axon to the mantle of the squid (114). It seems likely that other nerve fibers are responsible for more localized effects. However, no direct proof is yet available that the same muscle fibers are involved in the two contraction types.

Originally a system like that of *Branchiomma* must be considered to consist of different units which have fused together. In other giant fiber systems, which likewise function as a single unit, there is still a one-way transmission between the central part and the peripheral fibers (cephalopods, crustaceans). There are, however, other cases in which nervous structures function as one unit but for which the anatomical details are lacking. This is true for the nerve fibers innervating the retractors of the oral discs in sea anemones [Pantin

(63)] and especially in the subumbrellar nerve ring of the scyphomedusa. Kinoshita (51) showed that in ring preparations of *Mastigias papua*, cooling could lead to a state in which the nerve impulse circles twice as fast as the muscle contracts. This happened when the temperature was so low that nerve conduction was possible, but the refractory period of the muscle was so long that it could respond only every other time.

In the legs of the decapod crustaceans, the number of nerve fibers innervating the seven muscles moving the three distal joints has been worked out, and exact figures can be given [Wiersma (99, 102, 102a)]. The motor innervation has been found to be the same in all four tribes: Palinura, Astacura, Anomura and Brachyura. Three muscles have a monaxonic motor innervation, three a diaxonic, and the seventh receives four motor fibers. Since two of the monaxonic muscles are innervated by the same nerve fiber, 12 motor fibers form the complete innervation for these seven muscles. In addition to these motor fibers, every muscle receives a branch of at least one inhibitory fiber. In the Brachyura and in the coconut crab (Anomura) two muscles receive branches of two inhibitory axons. In total there are only three inhibitors for the seven muscles, whereas in Astacura this number may be four. The way in which these fibers branch is different in the different tribes. In *Birgus*, one of them sends branches to all seven muscles, whereas each of the other two go to one muscle only. These findings contradict the older view that inhibition would play an important part in the co-ordination of the muscular movements. Only in the case of the two muscles which share a single common motor axon is the function of inhibition clear. In all instances, each receives a branch of an inhibitor which does not innervate the other; hence, notwithstanding the common motor fiber, the muscles can contract independently by appropriate inhibition.

Innervation by a limited number of fibers is not limited to the leg musculature but is also present in the muscles of the body. Wiersma (101) has described some preparations in which only a few fibers were found. There are indications that in some cases two peripheral root fibers of different ganglia may innervate single muscle fibers.

For insects, Pringle's (67) data show that each leg muscle receives only a few fibers, but a more exact isolation will have to be performed before the actual number is ascertained. This is especially so because it is doubtful whether inhibitory fibers are present in the insects. Pringle could not find any indication of peripheral inhibition in the cockroach, whereas Friedrich (32) considers that he proved its existence in *Dixippus*.

Facilitation.—The transmission mechanism between nerve and muscle is often subject to a facilitation mechanism. In sea anemones, this process has been studied by Pantin and his school. It was found that there are important differences in facilitation between different muscles of a given species. In the retractors of the oral disc a single impulse is inactive. Facilitation occurs when a second impulse follows the first within 3 sec. Subsequent impulses result in increasingly larger contractions. In the case of the parietal and the

isolated circular muscles, another type of facilitation is present [Pantin (65)]. The contraction which occurs in these muscles only after a number of stimuli have been given is invariably delayed for a long time and is completely smooth; incompletely fused contractions, such as the contractions the retractor muscle exhibits at low frequencies of stimulation, are never obtained. There is also a marked influence on the resulting contraction from the activity of the animal at the time of stimulation, with indication of reciprocal inhibition between the circular and parietal muscles. Activity of the circular muscles in the whole animal is always initiated at the oral end, traveling towards the foot as a peristaltic wave. In the whole animal, stimulation of the body wall never results in contraction of the circular muscles under the electrodes; instead, the parietal muscles contract first.

In the ring muscle of the jellyfish, facilitation comparable to that of the retractor muscles of the sea anemone has been observed by Bullock (21). The difference is that a single stimulus does elicit a contraction whose height is increased by repetition of the stimulus [see also Kinosita (51)].

In the arthropods, the process of facilitation is better understood than in the other phyla. In these animals, the amount of facilitation depends on the "system" involved. The easiest to describe and the ones about which there is the least controversy are the "slow" systems. For these, it has been proven that repetition of the nerve impulses leads to increasingly larger local potentials which are accompanied by a gradually increasing contraction. Since the nerve fiber ends at many places on each muscle fiber, these local contractions can, on high frequency stimulation, lead to very powerful contractions. According to Wiersma & Wright (106), a similar mechanism is responsible for all types of fast contraction. However, in some cases of fast systems, the first muscle action potential is maximal and no facilitation can be observed. In the latter instance, there is usually a twitch on a single impulse, whereas, in the other fast systems, two or more impulses are needed before contraction occurs. Katz & Kuffler (50), on the other hand, are of the opinion that from a certain threshold onwards, conducted muscle action potentials arise so that a "recruitment" of fibers would occur for this process. Katz (49) has recently reviewed this subject and little needs to be added to it. However, it may be pointed out that the quintessence of the argument is whether the conducted action potential found by Katz & Kuffler is really comparable to the one of vertebrate striated muscle. According to Wiersma & Wright, the potential would always be limited to the innervated side of the muscle fiber because it is not possible to lead off negative potentials from the non-innervated side. A theoretical solution, in accord with all data thus far obtained, would be that the large local potentials which arise at a fast nerve ending would be strong enough to stimulate the next section of the sublemnial fast fiber. In this way, its nerve ending would again cause a large local potential, stimulating the next stretch of the sublemnial fiber, and so on. Such a conducted potential would be restricted to the innervated side of the muscle fiber. Since normally all the sublemnial branches would

be stimulated at about the same time, this type of conduction would be almost completely restricted to artificial conditions.

Boardman & Collier (12) investigated the effects of low magnesium content of the perfusion fluid on facilitation in the crab, *Carcinus*. As does Waterman (97), they find that decreased magnesium enhances facilitation. However, below a certain level, the transmission becomes blocked in *Carcinus*. Waterman reports maximal enhancement of facilitation in the absence of any magnesium in the crab, *Maia*, as well as in the crayfish. Waterman (97) also found that potassium has an enhancing effect on the fast twitch of the crayfish in a concentration at which the slow contraction is depressed.

In insect leg muscles, a fast system is present which causes a twitch contraction on a single impulse. Roeder & Weiant (79, 80) have shown that each muscle fiber is multiply innervated by branches of the fast axon. The muscle action potentials of this system are all or none in character. However, they must be local, since when one electrode is put on the muscle surface a positive potential is always obtained. When two impulses are given in quick succession, the muscle action potentials do not fuse, as do those of the fast closer system of the crayfish; on the contrary, the second action potential is reduced in amplitude. Another difference with the crayfish is that nerve degeneration is possible. Three to five days after cutting the nerve, the muscle is no longer electrically excitable. Pringle (67, 68) had shown that in other leg muscles of the roach, smaller potentials which show facilitation can be obtained by selective stimulation. Compared to the slow system of the Crustacea, the first impulse has a larger electrical effect. A more important difference is that the frequency necessary to obtain a mechanical effect is much higher, about 30 as against about 2 per second.

In other phyla, facilitation and summation of muscle action potentials have also been reported, but no nerve fiber isolation has yet been possible. In the anterior retractor muscle of the byssus of *Mytilus*, Fletcher (30) found summation and facilitation of the action potentials on direct stimulation of the muscle. Two types of muscle action potentials have also been reported for the columella muscle of *Helix*, one fast, the other slow [Bozler (18); Ramsay (74)]. Lately, Prosser *et al.* (71) have found fast and slow potentials present in the muscles of the proboscis of *Phascolosoma* and in the latern retractors of *Thyone*. In all these cases, only the slow potential shows summation and facilitation, whereas the fast action potential shows quick fatigue. In the body wall of *Thyone*, only fast potentials are found, while in the retractors of *Mytilus* only slow ones occur. Prosser *et al.* believe that two different muscular conduction systems are responsible for these differences, rather than two types of nerve fibers. In this connection, experiments by Schwab (83) may be mentioned, in which the spread of excitation in leech muscle was determined. In ventral strips with nervous system, conduction was found to be slower (20 cm. per sec.) than in dorsal ones (50 cm. per sec.).

Spacing effect of nerve impulses.—This effect, perhaps more of theoretic-

cal than of practical interest, is a result of certain peculiarities of the facilitation shown by decapod nerve-muscle systems. Wiersma & Adams (104) found that in certain muscles the same number of impulses per second might give a considerable contraction when delivered in pairs, whereas equally spaced ones failed to have a mechanical effect. This was the case only in part of the nerve-muscle systems. In slow systems, there is either no difference at all between the contractions, or if present, it is very small. In fast systems, it is only present in those in which a single nerve impulse does not result in a twitch. The closer the two impulses in each pair are together the greater the effect, up to the limit set by the refractory period of the nerve fiber. Theoretically, therefore, it is possible that a contraction of a given magnitude can be maintained by a much smaller number of spaced impulses than would be necessary to maintain the same contraction by regularly spaced ones. Wiersma (103), studying the innervation of the monaxonic opener muscle of the hermit crab, *Eupagurus*, has come to the conclusion that in this muscle two types of nerve endings are present on each muscle fiber. One type, not sensitive to spacing, gives rise to slow contractions. The other type is sensitive to spacing and brings about fast contractions. The innervation of this muscle may be considered to have the same elements as many muscles with two motor axons, but here the endings are excited by the same nerve fiber.

Inhibition.—The inhibition in the decapod Crustacea has been investigated recently by Kuffler & Katz (54). In general, their findings agree with those of Marmont & Wiersma (56). They, too, failed to find any marked potential change in the muscle when the inhibitory fiber alone is stimulated. They confirm that two types of inhibition are possible, one with reduction of the action potential of the muscle and one without. Reduction takes place only when the inhibitory impulse arrives shortly before the excitatory one. Wiersma & Ellis (105) have shown that, in many muscles, no reduction of the action potential takes place during inhibition, even when the inhibitory impulse precedes the motor one slightly. Kuffler & Katz report reduction of action potentials in a doubly motor-innervated muscle, whereas previously, such reduction had been limited to part of the monaxonic muscles. Wiersma & Zawadzki (107) found that magnesium did not influence the inhibitory mechanism. It did not become easier to inhibit contractions of the opener of the crayfish after they had been reduced by high magnesium concentration. Inhibition remains a mystery; especially the way in which it is possible to inhibit contractions without reduction of the muscle action potential. As noted, inhibitory phenomena are present in other phyla, but insufficient is known to permit comparison.

Insect flight muscle.—The compatibility of the very high frequency of the wing beat shown by certain insects with the contraction and relaxation times of muscles has been an outstanding question. The experiments performed do not really provide an answer, as yet, but rather show the way in which an answer must be sought. Pringle (69) was the first to notice that in

indirect flight muscles of flies, the action potentials of the dorsal longitudinal muscles in the thorax have a much lower frequency than the wing beats. This discrepancy is enhanced when the wing beat is made higher by removing part or all of the wing. The beat frequency increases, while that of action potentials decreases and under extreme conditions there may be one action potential per 40 beats. These results have been fully confirmed by Roeder (76), who has found the same mechanism in the Hymenoptera. On the other hand, by no means all flight muscles show this phenomenon. It is absent even in such good fliers as the sphingids among the moths (unpublished), as it is in the representatives of the Lepidoptera and Orthoptera which have been studied [Roeder (77)]. In the latter animals, it is possible to obtain muscle contractions by stimulating the appropriate nerves whereas, in the Diptera and Hymenoptera, nerve stimulation does not lead to contraction of the flight muscles. Pringle (69) and Roeder (77) have both come to the conclusion that for the muscles of the latter, two factors must be present for contraction. One is the nervous impulse, the other muscular stretch. Contraction of either group of indirect flight muscles would, according to them, deform the thorax in such a manner that the antagonists are of necessity stretched. This stretch is considered to be a stimulus for the muscle fibers to contract. In the absence of nerve impulses, as at the end of flight, a gradual decrease in the neurogenic factor would take place and the wing movements would die out. Assuming that this mechanism would work, one main question remains unanswered. How does the first muscle contraction arise when no stretch is present? It may be that accessory muscles would provide the stretch, but this has not yet been proven. There are, of course, other cases in which stretch is believed to be a controlling factor in muscular contraction. Von Uexküll (93) for instance, considers it to be the mechanism by which the co-ordinated movements of sea urchin spines are brought about. However, it should be pointed out that the great difference in time scale and the behavior of the action potential in insects raises the question of the validity of such comparison. According to Boettiger & Furshpan (14, 15), a mechanical device would at least be partially involved in this reciprocally contracting mechanism. At both anatomical limits of movement, the wings would be temporarily locked in position by the structural nature of the wing base. The muscles would first contract isometrically until the resistance was overcome, and then shorten considerably, stretching the antagonist. Nevertheless, such a mechanism can not be of great importance with regard to the frequency of the wing beat, as this remains fairly constant from the first beat onwards, including that of the damped beats at the end of flight when the wing no longer reaches the extreme positions. Another experiment of Boettiger, reported by Roeder (77), concerns the crane fly in which, under normal wing load, the number of action potentials is about the same as that of the wing beats, although not as regularly spaced. On removal of the wings the number of potentials remains the same but the frequency of the wing beat increases so that there is no longer

any correspondence between the two. As Roeder has pointed out, further experiments, especially with stretched muscles, will have to be performed in order to find a more definite solution for this intriguing problem.

The flight muscles of the Diptera and Hymenoptera show definite structural peculiarities, as illustrated by the findings of Wanatabe & Williams (96) who report the presence of spherical bodies called sarcosomes, of 1 to 4μ in diameter, in the dorsal thoracic muscles of the blowfly. These bodies have a high titer of cytochromes as well as of other enzymes. They consider the bodies to be the equivalent of mitochondria.

Wing beat frequencies have often been determined. Sotavalta (89) presents a review of older literature and gives the flight tone of a large number of insects, determined by comparing the sound with stroboscopic observation and oscillographic recording. Williams & Galambos (108) performed similar experiments with *Drosophila funebris*. The normal frequency was about 180 per sec., and increased to about 260 after clipping the wings to one third of their length. They paid special attention to the frequency at the start and at the end of a flight and found no significant changes.

TONE

Tone, the presence of a long maintained tension in a muscle, has been ascribed to different factors. In the opinion of Ritchie (75), Bozler (20), and others, all tone is due to a tetanus. In smooth muscle, only a few nerve impulses would be needed to maintain a tension because of the very slow relaxation. From this point of view, relaxation always is considered to be passive. There are, however, arguments against this, like the ones quoted above for the byssal retractor muscle of *Mytilus*, which relaxes actively from a "tonic" contraction on stimulation of the muscle or the ganglion with faradic current. Hill has recently acknowledged this difficulty (38). By accepting, for this type of preparation, the existence of two types of nerve fibers causing contraction or relaxation, an explanation for the "catch" mechanism of tone would be available. This mechanism has been found in such muscles as the slow part of the adductors of the pelecypods, the byssal retractor of *Mytilus*, and the tonic muscles of the sea urchin spines. All these muscles may be considered as "long-fibered" and at least at one end there is a definite attachment. In the resting condition, these muscles behave differently on loading than do short-fibered "hollow-organ" muscles, as shown, for example, by Nieuwenhoven (61), for the byssal retractor.

The "hollow-organ" muscles are, in general, short-fibered. On loading, a considerable dislocation of the muscle fibers with respect to each other takes place. This has been well demonstrated by the investigations of Batham & Pantin (10) concerning the body wall musculature of the sea anemone. The circular muscle fibers can be stretched to about four times their length by filling the animal with sea water. At the same time, a considerable change occurs in the mesoglea which consists of two layers. The outer layer never shows folds, becoming thinner on stretching and thicker

on contraction. The inner layer with the circular muscle fibers shows buckling on contraction, which leads to crowding together of the muscle fibers. On stretching the animal, a straightening out of the inner mesoglea layer takes place, and in extreme stretching, all muscle fibers are located in a single layer with some space between them. In extreme contraction of the animal, the whole body wall can also fold. As these authors point out, the properties of the mesoglea must have an influence on the behavior of this muscle against stretch. It may be stated that to consider the muscle fibrils or the myosin threads as the only elements involved in relaxation, and especially in stretching, is an unwarranted simplification. The cutis of the seacucumber, studied by Jordan (46), who considers it as a changed muscular tissue, shows properties very much like those of the mesoglea. It may well be possible that a similar structural element is involved in other cases in which "viscoid" tone is present. The relation between the tensions developed on stretch by the muscle fibers and by the "inert" tissue will then govern the peculiarities of the tension-time relations which have been studied by Jordan and his school. The fact that these muscle fibers can undergo such great changes in length means, however, that in any event there remains a problem with regard to their structure. According to Postma (66), these fibers too, would have a "catch" mechanism and would be supplied by two types of nerve fibers.

It has often been considered that there may be two substrates present within one muscle fiber; one for phasic the other for tonic contractions. Bozler (17, 19) found in the muscle fibers which expand the chromatophores of cephalopods definite histological evidence for the presence of two substrates in the form of two types of fibrils in the same muscle fibers. For this muscle, Bozler (20) has been unable to give a satisfactory explanation in the terms he uses for other muscles. Lately, Winterstein (109) has come to the conclusion that in both frog heart and the dorsal muscle of the leech two substrates must be present.

Ozer & Winterstein (62) have studied the effect of different salt concentrations on the tone and oxygen uptake of leech muscle. They found that there is a certain sodium chloride concentration at which the muscle is most relaxed (.05 *N*). Both increase and decrease of the concentration causes contraction. For glucose, the greatest relaxation is at 1 *N*. Calcium always causes relaxation, whereas potassium gives either relaxation or contraction according to concentration. Hypertonic sodium chloride solutions cause strong increases in tone with diminished oxygen consumption. Potassium chloride addition always produces a greatly diminished oxygen uptake whether it increases or decreases the tone. The increased oxygen uptake on stimulation is also diminished by potassium chloride. Glucose, on the other hand, diminishes both tone and oxygen uptake. They come to the conclusion that "tonus and contractions by stimulation are entirely independent phenomena." Singh, & Singh (85), from experiments on the influence of ions on the retractor muscle of the byssus of *Mytilus* and on frog stomach,

have arrived at a similar result. Two contraction types are distinguished. One would be due to the release of neuro-humors, such as acetylcholine, which are rapidly destroyed, the other, tonic in character, would be due to an ionic effect. They believe that in the tonic system at least, relaxation is an active process.

Even in crustaceans the tone problem is not completely absent. Usually the relaxation of the fast and slow contraction is about equal, and inhibition has but little influence upon the relaxation speed. However, of the four contraction types present in the quintuply innervated flexor muscle of *Panuliris*, the second fastest one relaxes more slowly than the others. Its relaxation could be markedly speeded up by simultaneous inhibition [Van Harreveld & Wiersma (94)].

A problem which has received relatively little attention with regard to tone but which may be of great importance, is that of spontaneous muscular activity. In vertebrate intestinal muscle, myogenic origination of movement is generally accepted. Batham & Pantin (8, 9) consider it to explain the very slow conduction and the slow movements present in the sea anemone. Other indications of its occurrence may be found in observations such as those of Floyd (31), who found that the dorsal musculature of the earthworm gives spontaneous contractions. In flatworms, such a mechanism would seem likely, but Baldwin & Moyle consider the contractions they have been able to obtain from preparations of *Ascaris* to be of neurogenic origin. (4).

Turgor.—As has been pointed out lately by Batham & Pantin (8) and as had been realized earlier for "hollow-organ" animals by Jordan (46), the pressure of the fluid inside the "organ" will be of importance to all muscles surrounding it. When the fluid is free to flow through the whole body cavity, every muscle of the body wall will be affected by the contraction of any part. In cases where the fluid is "compartmentized," as in the annelids with complete septa, smaller areas will be affected. The tensions developed have been measured in a number of animals. Bantham & Pantin determined the pressure in the coelenteron of the sea anemone *Metridium* (8). They found during rest very low pressures of only a few millimeters of water. The largest rise occurred on contraction of the retractor muscles. Unless water is permitted to escape through the mouth, this pressure stretches the body wall considerably. They found that on introducing water artificially and thus enhancing the "turgor," the total motion of the animal for a given muscular contraction was much less than at a lower "turgor" level.

Zuckerkindl (116) measured the pressures in *Sipunculus* and *Phascolosoma*. The minimum is a few centimeters of water. During movements, and especially during digging, much higher pressures occur. The highest tension is developed when the animal goes into defense immobility by contraction of the longitudinal muscles; the pressure may then reach 100 cm. Chapman & Newell (24) studied the pressures in *Arenicola* and found a relatively high resting one (14 cm.) which, on narcosis, decreased to 3 cm., showing that even during rest the muscles must develop tension. During

burrowing and other movements, increases to about double the resting value occur, but they come to the conclusion that these pressures are not enough for digging into sand. Digging in hard sand would be made possible by the admixture of water. Newell (59) measured the pressure in earthworms and finds it larger in the anterior segments (15 cm.) than in the posterior ones (8 cm.). He describes the musculature of the septa which would be responsible for limiting the pressure changes to the part of the body in which the contraction occurs. Chapman (23) made calculations about the forces involved in the movement of worms. Smith (86, 87, 88) describes the mechanics of the tube feet of echinoderms in which fluid movement and the accompanying pressures play an important part in the extension which is caused by a contraction of two muscles in the ampulla. Pantin (64) gives as an example of the mutual influence which muscles in this type of animal can have on each other, the mechanism by which contraction of the circular layer of muscles of the body wall extends the proboscis by fluid pressure in the nemertean, *Geonemertes dendyi*.

PHARMACOLOGY

Of the invertebrate musculature, that of annelids seems to be most similar to that of vertebrates in its reaction to drugs. Ambache *et al.* (1) showed that acetylcholine contracts the gut, even after cooling has suppressed the supposedly neurogenic spontaneous movements. Atropine blocks these acetylcholine-induced contractions. The influence of ions on this preparation depends on temperature. Potassium gives contraction in the warm preparation, and this is enhanced by eserine and not blocked by atropine or nicotine. In cooled preparations potassium inhibits contraction. Calcium was found to inhibit the spontaneous contractions but not the acetylcholine contractions of cooled muscles. Barium in small amounts inhibits contraction in warm preparations but does not act at all on cooled ones. Previously, Millott (58) had shown that ergotamine antagonizes the action of the inhibitory fibers, atropine that of the accelerating ones.

Floyd (31), using the body wall musculature of the earthworm, finds that dorsal and ventral strips, the former without central nervous system attached, perform spontaneous movements. Cocaine and alcohol reversibly suppress the rhythm. These findings and the earlier ones of Wu (112) and Botsford (16) leave little doubt that a cholinergic mechanism is present in the transmission of the body wall musculature, although according to Bacq & Coppée (3), curare gives only partial block.

In the other phyla, no recent work has been noticed except in coelenterates and arthropods—the two groups in which the pharmacological reactions differ most from vertebrates. Ross (81, 82) has investigated the influence of drugs on the facilitation of the retractors of the marginal sphincter of the sea anemone, *Calliactis*. He found acetylcholine, eserine, and curare without effect. The only substance which gave a noticeable enhancement of facilitation and made the first shock active was tyramine. In testing extracts of sea

anemones, an active substance was obtained which differed in its effect from tyramine. As in crustaceans and insects, drugs like strychnine, histamine, epinephrine, and related substances are without effect. Veratrine does not act in sea anemones, whereas in Crustacea it is a powerful drug [Ellis *et al.* (29)]. Wright (111) has found that erythroidin and, in high concentrations, curare, have an effect on the neuro-muscular transmission in the crayfish. Using fast and slow closer contractions, he found that the fast twitch caused by a single impulse in the fast fiber was blocked at a time when faradic stimulation of the slow fiber still gave practically normal contractions. With higher concentrations and longer times, the latter was also depressed. When blocking occurred, direct stimulation caused contraction. This is considered to prove that the neuro-muscular transmitting mechanism is affected.

Edwards *et al.* (28) report ryanodine as a substance which causes a contraction of the muscular substance in all striated muscles, including those of insects. Several papers have appeared on the effect of 1,1,1-trichloro-2,2-bis (*p*-chlorophenyl)-ethane (DDT) on the neuromuscular system of arthropods (13, 91, 113). From the articles of Welsh & Gordon (98) and Roeder & Weiant (78) it seems clear that this drug, like many others, causes repetitive discharges in the nerve fibers. This effect is responsible for the results obtained in isolated legs, but it has a higher threshold than other phenomena caused by the drug [Dresden (26)].

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PHYSIOLOGY OF THE DIGESTIVE SYSTEM¹

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FOOD AND WATER INTAKE

Systematic knowledge of the factors governing food and water intake is difficult to obtain because of the interlacing of psychogenic, pathologic and physiologic factors. Excessive hunger may often be the result of unsuspected cerebral or hypothalamic disorders [Kirschbaum (1)]. Janowitz & Grossman (2) found that the average daily volume of food ingested by dogs was not significantly modified by feeding small portions of sucrose solution, cream, casein hydrolyzate, alcohol, or bitters 20 min. before the regular feeding. They also found that bulk rather than caloric content was the factor which diminished further food intake since the same bulk of cream containing from 73 to 172 per cent of the average daily caloric intake caused approximately the same decrease in food intake as a sucrose solution containing only 22 to 26 per cent of the daily caloric intake. They concluded that the physiological release of enterogastrone is probably not involved in the production of satiety. In a study on rats in which appetite was increased with insulin, Soulaire (3) concluded that the appetite for glucose is not dependent on gastric contractions but on hypoglycemia. Strang (4) studied the daily mass exchange in relation to satiety and found that a mass exchange approximating an intake of 5 per cent of the body weight and a urine output of 3 per cent of the bodyweight produces satiety. Thin people who maintained their weight had ratios quite normal while a group of obese subjects who were not quite in weight maintenance had ratios lower than normal. He found that the ratios of mass load are independent of energy load, thus confirming the finding of Janowitz & Grossman cited above. This method of study deserves further study and expansion.

Holmes & Gregersen (5, 6) stimulated thirst by the intravenous injection of hypertonic solutions. With saline solution, they found that thirst is not governed by the level of sodium or chloride in the blood, hence, the amount of water ingested is not the amount required to dilute the injected salt to isotonicity. They found that, whereas repeated tests on the same dog were quite consistent from day to day and varied directly with the amount of salt injected, great individual variations occurred in different dogs receiving comparable doses of salt. This finding suggests that previous conditioning and habit patterns may predominate over the purely physiochemical changes in water and electrolyte balance.

¹ The survey of the literature pertaining to this review was concluded in June, 1951.

SALIVA

In 1949, Ternberg & Eakin (259) discovered apoerythrin, a protein fraction found in normal gastric juice which protects vitamin B₁₂ from digestive destruction but which is inactivated by the gastric juice of pernicious anemia patients unless hydrochloric acid is added. It may be identical with or actually be the intrinsic factor of Castle. Apoerythrin is present in saliva of both normal individuals and pernicious anemia patients. Beerstecher & Altgelt (7) investigated the amount and variation in the saliva of 20 normal subjects. They found that the amount tends to diminish around meal times, suggesting a limited amount available for secretion. A high degree of individual difference was found in the amount and fluctuations.

While investigating the relationship of saliva to dental caries, Granados, Glavind & Dam (8) noted that hamsters which drank water containing human saliva grew more rapidly than controls. Further investigation by Granados, Glavind, Noer & Dam (9) showed that this growth promoting factor is different from the chemically known vitamins and vitamin B₁₂. Wu & Wu (10) have refined the method of collection and the determination of urea plus ammonia nitrogen in saliva, so that constant and reproducible values can be obtained. This technique may prove useful in studying the mechanism of salivary secretion and suggests the possibility of developing a urea clearance test for the salivary glands. Seltsam, Lanni & Beard (11) described a technique for collecting parotid separate from the submaxillary plus sublingual saliva and observed certain immunological differences in these fractions. An interesting, although familiarly stereotyped discussion, of the psychoanalytic aspects of hypersalivation was presented by Szasz (12). A study of the mechanism of regeneration of the submaxillary gland of rats after partial excision was made by Milstein (13). Many interesting papers on the relation of saliva to dental caries have been omitted because of space limitation.

TASTE

Cardullo & Holt (14) showed that the ability to taste or not taste phenylthiocarbamide is demonstrated in early infancy, even in premature infants. It is easy to demonstrate and to quantitate roughly the result. They suggest that the test could be used in cases of doubtful paternity where a tasting child is born to a nontasting mother. The ability to taste PTC was tested on the primitive Maoris of Australia and the percentage of tasters found to be 91.7 per cent [Simmons, Graydon, Semple & Taylor (15)]. Dethier (16) tested the taste sensitivity to compounds of a homologous series and found that the threshold concentrations decreased logarithmically as the glycol carbon chain is lengthened. Wright (17) showed that, contrary to prevailing concepts, denervated taste buds may remain intact for many months.

ESOPHAGUS

In a study on experimental esophagitis, Ferguson *et al.* (18) found that the contact of acid gastric juice with esophageal mucosa has a very prompt

and pronounced destructive effect. The damaging effect is not due to the acid concentration per se but to the peptic activity. The same acid pepsin concentration is much less damaging to intestinal mucosa.

The two following papers are of considerable importance to those interested in experimental surgery of the esophagus. Macmanus, Dameron & Paine (19) made a systematic study of the extent to which one may interfere with the blood supply of different portions of the esophagus and obtain healing on anastomosis. They found, for example, that necrosis of the dog esophagus does not occur following complete devascularization of the thoracic portion, division, and anastomosis. Postlethwait *et al.* (20) studied the mechanical strength of end-to-end esophageal anastomosis and esophagogastric anastomosis at various periods after operation.

The psychosomatic aspects of cardiospasm were described by McMahon, Braceland & Moersch (21), and their discussion suggests several interesting experimental approaches employing condition reflex techniques. Van Wezel (22) reported a case in which two intense esophageal spasms, lasting from 5 to 10 min. and not relieved by atropine or amyl nitrite, were brought on by drinking cold fluids, but not by immersing the hands in ice water.

Williams (23) studied esophageal sensation, tested by balloon distension, in patients after complete or partial sympathectomy. There was no evidence that sympathectomy impaired this type of sensation. A cinefluorographic study of swallowing in human subjects was made by Rushmer & Hendron (24). They believe that their findings cannot be fitted into the usual description of three stages. "On the contrary, deglutition is more conveniently described as a series of functional events." It appears, however, that their findings in general confirm the classical description of Magendie.

STOMACH

Acid secretion.—Gudiksen (25) made a very extensive study of the electrolytes in fundic gastric secretions obtained from anesthetized cats using histamine, pilocarpine, and electrical excitation of the vagi as stimuli. Attempts to study gastric secretion and emptying with test meals are in general crude and unsatisfactory, consequently, the studies of Hunt (26) and Hunt & Spurrell (27) are of great interest. They developed a pectin test meal containing phenol red. The content of phenol red, chloride, acid, and pepsin are determined in the gastric samples. A series of meals (from 5 to 12) are given to the same subject on different days and the stomach emptied completely at successive 15-min. periods for 2 hr. or more. The results from these multiple meals are then integrated to give a profile of the rate of emptying and secretion. The secretions are expressed as parietal and nonparietal. Since the total volume of meal plus secretions in the stomach is presumably known, the secretions can be expressed not only in terms of concentration, but also as total volumes. The possibility of determining the total volume of the secretions is of paramount importance and would give this meal a distinct advantage over that proposed by Wilhelmj. O'Brien & Hill (260). The method is ingenious, but since some of the calculations and interpreta-

tions are based on questionable assumptions, it should be carefully checked in isolated whole stomach pouches where the volume factor can be accurately controlled by known removal. A similar control should probably be done in the human stomach isolated from the duodenum by a balloon. The method appears to offer great promise as a research technique.

Woodward, Bigelow & Dragstedt (28) studied the effect of antrum removal on secretion from Pavlov pouches. They demonstrated the importance of complete removal, since removal of less than two-thirds may have no effect and even 90 per cent removal may be followed by considerable secretion. They point out, very correctly, that much of the confusion in the literature on this subject is due to the use of "free acid" values as an index of acid secretion. It may require another 50 years to eliminate this anachronism from the clinical laboratory, but it should certainly not be used as an index of secretion in scientific studies.

Dragstedt *et al.* (29, 30) made quantitative studies on the three phases of gastric secretion and found that in the dog the antral and vagal phases account for about 90 per cent (contributing nearly equally) and the intestinal phase for about 10 per cent. When the three phases are acting simultaneously or normally, the volume of secretion is greater than the sums of the secretions from individually isolated phases, thus suggesting potentiations between the phases. If the antrum is removed and exteriorized as a pouch so that the mucosa does not come in contact with the gastrointestinal contents, the secretion of Pavlov and whole stomach pouches falls to low levels; on the other hand, if it is anastomosed as a diverticulum on the duodenum or colon, marked hypersecretion occurs often accompanied by ulcers in the stomach.

In addition to direct contact of pyloric mucosa with secretagogues present in food, duodenal or colonic contents, what other mechanisms are involved in the liberation of gastrin? This question has been the subject of several interesting papers and controversies. Robertson *et al.* (31) showed that bathing the mucosa with acetylcholine caused liberation of gastrin. It has been reported that injection of acetylcholine into the arteries of the stomach failed to cause acid secretion. Pevsner (32) however, using unanesthetized dogs, showed that small doses (0.0006 to 0.6 mg. per hr.) injected intra-arterially constantly caused acid secretion while larger doses might not. Lim & Moser (33) studied dogs with three pouches, i.e., pyloric, Pavlov, and Heidenhein fundic pouches. The pyloric pouches were demyenterized (mucosa separated from the muscle and myenteric plexus). Mechanical (distension) or chemical (acetylcholine, histamine, or pilocarpine) stimulation of the pyloric muscoa caused liberation of gastrin. The mechanical stimulation was inhibited by cocaine or atropine locally and tetraethylammonium chloride intramuscularly. Because of the inhibiting effect of tetraethylammonium chloride, they believe that the secretion elicited by mechanical stimulation involves intramucosal nerve elements consisting of both afferent and efferent fibers. They suggest that this be called the adenoenteric or adenteric reflex.

Lim & Mozer (34) reinvestigated the problem of the liberation of pyloric gastrin by vagal stimulation. Dogs with pyloric, Pavlov, and Heidenhein fundic pouches were used. They repeatedly showed that sham feeding caused acid secretion in the Pavlov but not in the Heidenhein pouch. They stress the fact that vagally denervated fundic pouches are not suitable indicators of gastrin liberation. Their evidence indicated that vagal fibers acting on the pyloric cells cause liberation of minimal amounts of gastrin which may potentiate a minimal or subminimal vagal effect on the parietal cell and cause secretion. Cocainization of the pyloric mucosa inhibited the secretion of the Pavlov fundic pouches. The studies of Glass & Wolf (35) permit a similar conclusion.

The comprehensive studies of Linde (36) appear to confirm the earlier work of Uvnas in showing that vagal secretion is greatly diminished by resection, cocainization, or interference with the blood supply of the pylorus. It should be emphasized, however, that the conditions of the experiment were far from physiological and the rate of secretion very small; higher rates of secretion may have been more difficult to inhibit. Janowitz & Hollander (37) found that Heidenhein pouches failed to secrete acid following sham feeding or insulin but did secrete in response to histamine or food in the main stomach. They conclude that these facts are absolute evidence against the liberation of gastrin by vagal stimulation of the pylorus. It should be emphasized, however, that the difference between their results and those of Lim & Mozer could also be explained by the following considerations: Heidenhein pouches have a high threshold for all stimuli; histamine is a very powerful stimulus; food in the main stomach liberates large amounts of gastrin, while vagal stimulation of the pylorus liberates small amounts. In this connection, it is interesting to find that Noring (38) concludes that partial gastrectomy accomplishes the same result as vagotomy with respect to secretion of vagal origin. Langlois & Grossman (39) studied the effect of removal of the pylorus on the acid secreting response to other stimuli and conclude that their findings are in accordance with the hypothesis that cholinergic impulses release gastrin from the pylorus and potentiate the response of the parietal cells to other stimuli.

The effectiveness of Banthine (β -diethylaminoethylxanthene-9-carboxylate methobromide) in inhibiting acid secretion was studied by Benjamin, Rosiere & Grossman (40) who concluded that it blocks acid secretion by its atropine-like action. Smith *et al.* (41) found that Banthine markedly reduces the nocturnal secretion in peptic ulcer but that it does not abolish the response to insulin; from these facts, they question whether nocturnal secretion is of vagal origin as generally believed. Robertson *et al.* (42) studied the action of some xanthine derivatives and found that in some species certain of them will not cause secretion when given alone, but will potentiate or lower the threshold for other stimuli. Janowitz *et al.* (43) studied the response to sham feeding in a human subject; the results were in agreement with well-established facts. Kuzmenko (44) was able to study the three phases of gas-

tric secretion in human subjects undergoing a two-stage operation for correction of esophageal stenosis. He pointed out that the cephalic phase was abolished by pain or fear and that the intragastric phase was diminished by vagotomy. The first of these observations should be a warning that when the cephalic phase is being studied in animals, the same rigid precautions should be observed as Pavlov demanded in conditioned reflex studies in order to avoid distraction. Davenport & Chavre (45) reported further improvement on the *in vitro* mouse stomach preparation so that it now responds to histamine, distension, fat feeding, or injection of urogastone (the two latter before making the preparation) in the normal manner. They also reported that, when the pH of the internal fluid falls below 2.5, acid accumulation (secretion) stops; it is quite possible that this is due to the phenomenon of acid inhibition (261). Shafer & Kittle (46), using whole stomach pouches, report data which they interpret as showing that the sympathetic nerves exert a tonic inhibitory effect on gastric secretion. The gastric samples were collected for only 60 min. each morning, following 1,000 cc. of saline given intravenously. This short period of sampling is not sufficient to justify the conclusion, total 24 hr. collections would be necessary; also, the large intravenous injection of saline would probably influence the volume of secretion. Their finding is not in harmony with findings on human subjects after thoracolumbar sympathectomy.

Of interest to physiologists and clinicians is the study of Levin, Kirsner & Palmer (47), re-emphasizing the variability, unpredictability and dosage independence of the effect of atropine on the fasting gastric secretion of peptic ulcer. Rehm *et al.* (48) and Coy *et al.* (49) have continued their studies on the significance of and the factors influencing the electromotive forces set up during gastric secretion. Rosiere & Grossman (50) reported that an analogue of histamine, 3-(β -ethylamine)-pyrazole, stimulates gastric acid secretion but lacks the circulatory effects of histamine. Mahl (51) presented some very interesting observations on the relationship of anxiety to acid secretion. It was also shown (52) that reflexes from the large intestine may influence acid secretion. Segal *et al.* (53) described an indirect method of determining the presence or absence of free acid in the stomach which may prove useful in experimental studies.

Mucus secretion.—Most investigators now agree that there are at least two dissolved mucus fractions in gastric juice: mucoprotein secreted by the mucus cells of the neck of the gastric glands, and mucoproteose which is a disintegration product derived from the surface epithelium. Glass & Boyd (54), continuing their valuable studies on gastric mucin and its fractions, compared the stimulating effect of prostigmine, mecholyl, and pilocarpine with insulin and found the first three to be very variable and inconstant in their effects, whereas the stimulating effect of insulin was very constant and uniform. The same authors (55) studied the response to insulin of a group of normal subjects and patients with various gastric diseases and described the pattern of response of gastric mucin. Glass *et al.* (56) and Gray *et al.* (57)

found that gastric mucoprotein is absent from the gastric secretion in pernicious anemia while mucoprotease is present, a finding to be expected in view of the marked atrophy of the gastric glands. Janowitz, Hollander & Jackson (58) reported that topical application of acetylcholine, mecholyl, or pilocarpine to the mucosa of Heidenhein pouches leads to a copious secretion of a very viscid, opalescent, cell-free mucus with a pH between 7.0 and 7.5. The effect of histamine on the secretion of mucoprotein appears somewhat doubtful since Gray *et al.* (57) found marked stimulation while Grossberg, Komarov & Shay (59) stated that it inhibits both mucoprotein and mucoprotease secretion. Gray *et al.* found that the mucoprotease fraction was diminished.

The studies of Glass, Pugh & Wolf (60) suggested that the alkalinity and buffering power of gastric mucus is due to dialyzable substances including mineral bases and not to the mucus itself. A detailed study of the electrophoretic patterns of the proteins of canine gastric juice was made by Grossberg, Komarov & Shay (61). In a preliminary report, Glass *et al.* (62) have presented rather striking evidence suggesting that human gastric mucoprotein either contains or is identical with the intrinsic antipernicious anemia factor of Castle (see also the section on SALIVA in this review). Sober, Hollander & Sonnenblick (63) repeatedly applied a strong chemical irritant (5 per cent eugenol solution) to the mucosa of a Heidenhein pouch and found, in agreement with well-known principles, that mucus secretion at first high, gradually diminished and an inflammatory exudate appeared. Even after three to five months, recovery was still incomplete. Glass *et al.* (64) studied the effect of vagotomy and gastric resection on mucin secretion. After resection, they found an increase in mucoprotease, which they believe is due to gastritis and a decrease in the total output but not the concentration of mucoprotein. After vagotomy, the secretion of mucoprotein was completely abolished, and no increase occurred after insulin.

Secretion; general.—Linde & Obrink (65) studied the potassium content of histamine secretion and found that the concentration is practically unaffected by changes in rate of secretion and, therefore, concluded that the output is directly proportional to the volume of secretion. Martin (66) emphasized that, since the potassium concentration of saliva and gastric juice is higher than that of serum, continued loss of gastric juice may cause potassium depletion.

Sharick & Campbell (67) studied gastric secretion during insulin shock therapy in human subjects and found that high doses of insulin and very low levels of blood sugar do not inhibit secretion as was found by Necheles, Olson & Scruggs in dogs (262). Code (68) presented an excellent review on the inhibition of gastric secretion.

Motility.—Lorber, Komarov & Shay (69) studied the effect of sham feeding on gastric motor activity. The final and predominate effects preceded and lasted as long as the secretory response. These effects were an increase in fundic tonus, decrease in antral tonus, and cessation of peristaltic waves;

in other words, practically the same initial changes that would have occurred had the food entered the stomach. Hightower *et al.* (70, 71) studied antral motility in normal and vagotomized human subjects. No significant effect on antral gastric motility followed sympathectomy in human subjects [Morlock *et al.* (72)]. Some of the last papers by the late B. P. Babkin dealt with the effect of the cerebral cortex and central nervous system on gastric motility (73, 74, 75).

Vagotomy.—The long time effect of vagotomy on acid secretion seems highly debatable. Dragstedt, Woodward & Camp (76) found no evidence of return to normal in humans or animals. Walters & Belding (77, 78) found a return to normal in one to four years after vagotomy alone in about 24 per cent of cases, but when gastroenterostomy or partial resection was combined with vagotomy, in only 7 per cent. Priviteri (79) found an initial drop but a return toward normal in the next two years. In a one- and two-year follow up on dogs, Postlethwait *et al.* (80) and Deaton *et al.* (81) found a diminished response to histamine and Urecholine (urethane of β -methylcholine chloride; bethanechol) but no response to insulin. Cornell (82) in an 11 year follow up on one patient found the acid response still low after several years. These differences are logical, in fact, predictable, when analyzed with the following factors in mind: (a) the known interrelationships between the vagal and gastric phases of acid secretion, (b) the variable and often inaccurate analytical techniques used (free acid), and (c) the different types of stimuli employed.

All of the above mentioned investigators found a decrease in gastric motility or delayed emptying time. Dragstedt & Woodward (83) now agree with most observers that vagotomy should be combined with gastroenterostomy to facilitate emptying. The pseudoscientific findings and speculations regarding changes in glucose tolerance after vagotomy are doubtless due to changes in emptying time since Adams (84) found no pre- and post-operative differences when glucose was administered intravenously.

Miscellaneous.—Benjamin (85) presented an unusual and provocative study on the neurovascular mechanisms of the stomach and duodenum which he believes may be important in the etiology of peptic ulcer. Miller *et al.* (86) re-emphasized the remarkable ability of gastric mucosa to regenerate functionally after very severe trauma.

Just how normal is the functional response of the conventional stomach pouch after being separated from the "gastrointestinal stream" for prolonged periods? This question has concerned most workers in the field of gastric physiology, and with this in mind, Olson, Walker & Necheles (87), by modernization of an old technique, devised a method in which the pouch is an integral part of the intestinal tract until used.

Studies on techniques for radiation of the gastric mucosa without radiation of other organs were reported by Douglas *et al.* (88) and by McKendry (89). The significance of urease in the gastric mucosa has been investigated by three groups (90, 91, 92) without very definite or unanimous conclusions.

Goodman, Ginsberg & Robinson (93) reported an improved apparatus for recording the electrogastrogram, and Mahlo (94) reported the electrogastrographic changes produced in several different ways.

DUODENUM

Hartiala, Ivy & Grossman (95) found that cinchophen caused a marked decrease in the volume, alkali content, and mucin content of the secretion from isolated duodenal pouches (Brunner's glands). They stated that work in progress shows that cinchophen also causes a decrease in pyloric mucus secretion. Thus, cinchophen would render both the pylorus and the upper duodenum vulnerable to ulcer formation because of the lack of protective secretions. Hartiala, Magee & Grossman (96) found that cinchophen caused an increase in both volume and alkali content of pancreatic juice. Apparently this latter effect usually offsets the depression of the secretion from Brunner's glands so that the duodenum is usually protected, leaving the pylorus as the vulnerable area where most cinchophen ulcers occur. This appears to be the first entirely satisfactory explanation for the location of most cinchophen ulcers in the canine pyloric region. Wilhelmj *et al.* (97) studied the acid-reducing mechanisms of the normal human duodenum and found that dilution is somewhat more important than neutralization. The acid-reducing capacity was remarkably constant over a period of several months in the same individuals. Under maximal stimulation, the total mixed duodenal secretions averaged from 500 to 1,100 cc. per hr. Nausea without retching or vomiting caused a marked decrease in the volume of the secretions.

EXPERIMENTAL ULCER

Production.—It has been repeatedly shown that spontaneous chronic peptic ulcer is extremely rare in dogs, but several investigators have pointed out that acute superficial ulceration, hemorrhagic erosions, and hemorrhagic gastroenteritis are often found in dogs dying a lingering death from a variety of causes. More recently, Selye has emphasized that similar lesions are non-specific as regards etiology and are a part of the alarm reaction. In view of these facts, it appears that Schaefer, Copeland & Salmon (98) were correct in questioning the specificity of the duodenal ulcers which they found in six of seven dogs maintained in choline deficient diets for prolonged periods of time. Poth *et al.* (99) made the surprising observation that normal and depancreatized dogs maintained in a state of chronic hypoglycemia were equally susceptible to ulcer formation. Poth & Fromm (100) subsequently showed that the hyperglycemic-glycogenolytic factor present in ordinary insulin was not a factor in these results. Here again, the question arises whether prolonged hypoglycemia, acting as a powerful alarm stimulus, was able to precipitate an alarm reaction which, nonspecifically, overshadowed the difference between the normal and depancreatized dogs.

In an excellent study on the genesis of gastroduodenal ulcer following burns, Friesen (101) concluded that of all the possible factors investigated,

hemoconcentration was the single most important one. The increased viscosity and decreased blood flow resulted in anoxia of the mucosa which was then increasingly susceptible to the digestive action of the acid-pepsin gastric secretion, which was not necessarily increased in amount or degree. Prevention of hemoconcentration by plasma injections prevented the formation of ulcer following burns, even when histamine in beeswax was injected.

Prevention.—The Mann-Williamson preparation is probably the most severe test object to which an ulcer-preventing procedure can be subjected; hence, the finding of Oliver (102) that bilateral vagotomy plus removal of the pylorus prevented ulcer while neither procedure alone did so indicates that this combined operation profoundly depresses gastric secretory function. Fogelson & Lobstein (103) found that a detergent complex (sodium alkyl sulfate bound to gastric mucin) prevented the ulcers caused by injection of histamine in beeswax. Since the gastric juice in these animals showed a decrease in total pepsin as well as pepsin concentration but no decrease in the concentration of acid, they focus attention on the disputed point of pepsin rather than acid as the important agent in producing this type of experimental ulcer. Cheney (104) reported an antipeptic ulcer factor present in cabbage and cabbage juice, fresh milk, and egg yolk. Nasio (105) reported that the intramuscular injection of magnesium chromoacetate will prevent cinchophen ulcers in dogs. The ubiquity of histamine in the animal organism and its possible participation in several facets of the ulcer problem made the study of Kittle, Batchelder & Schafer (106) a logical necessity. They found that, when histamine in beeswax was administered daily to gastrectomized dogs for from 21 to 40 days, no ulcers were found in any part of the gastrointestinal tract.

Vagotomy.—One of the most troublesome sequela of vagotomy in ulcer therapy is food retention in the stomach because of the slow emptying time. In a study on dogs, however, it was shown that the buffering action of the retained food was the most important factor in protection against histamine-beeswax ulcer and that any procedure which hastened emptying resulted in a higher incidence of stomal ulcerations [Lillehei, Lewis & Wangenstein (107)].

Healing.—Gunter (108), in a histological study of the healing of acute ulcers, found that the denuded area was covered with epithelium in three days but no mitotic figures were present; thus, it appears that ameoboid movement of the cells over the base is the first step in healing.

HUMAN ULCER

Etiology.—The attractive hypothesis that a deficiency of gastric mucin may be a cause of peptic ulcer has never been satisfactorily settled; consequently, the excellent study of Glass & Boyd (109) is of great importance. They found no evidence of a deficiency of gastric mucin or its fractions in the gastric juice of patients with gastric or duodenal ulcer, in fact, the mucoprotein fraction was increased. Their data are also evidence against the participation of the mucolytic enzyme lysozyme as an etiological factor.

Doll & Buck (110) studied the incidence of ulcer in the sibs and parents of 300 ulcer patients and concluded that hereditary factors are of importance. Two case reports (111, 112) which appear to challenge the clinical dictum "No acid, no ulcer" were discussed by Grossman (113). Levin, Kirsner & Palmer (114) and Kauvar & Leiter (115) call attention to pitfalls in the same problem. Wilhelmj *et al.* (97) studied the acid-reducing mechanism of the duodenum in two patients with duodenal ulcer and found that the quality and quantity of the secretions and the acid-reducing mechanisms were normal in a young man with a very acute ulcer (first episode) which healed promptly with medical treatment. In a chronic ulcer of several years duration and with frequent recurrences in an older patient, the duodenal secretions were normal in quality but greatly reduced in amount, hence the acid-reducing power of the duodenum was much below normal. The number of cases is too small to draw definite conclusions.

Pain.—Banthine (116 to 119) and tetraethylammonium chloride (120) have both been reported to bring prompt pain relief in ulcer. Thoracolumbar splanchnicectomy has been reported to interfere with pain sense in ulcer and extrahepatic biliary tract disease (121). Duodenal ulcer has been reported to cause discomfort but not actual pain in a patient after removal of the spinal cord with the exception of the cervical segment (122). These clinical observations indicate the need for further study of the pathways carrying the pain impulses in peptic ulcer.

Acid.—Not all clinical investigators are convinced that there is true nocturnal hypersecretion in peptic ulcer, but Zuckerman, Leiter & Kauvar (123) claimed its presence and stated that it paralleled the severity of the symptoms and, when high, was an indication that medical treatment would fail. Levin, Kirsner & Palmer (124) compared 16 normal and 16 duodenal ulcer patients and found very pronounced nocturnal hypersecretion in the latter. They stated that it remains unaltered with healing of the ulcer and believed it to be vagal in origin.

Diagnosis.—The usual gastric test meals are in general rather disappointing procedures and seldom give sharp clear cut information of definite diagnostic value. Any laboratory procedure which promises to fill this deficit deserves careful study. Janowitz, Levy & Hollander (125) investigated the excretion of uropepsin (urinary pepsinogen) which is derived from the stomach. They found it absent in pernicious anemia and after total gastrectomy and normal in gastric neoplasm and gastric ulcer. Patients with active duodenal or stomal ulcer, however, excreted on the average of four times as much as normal subjects. This factor should also be investigated in experimentally produced ulcers.

Treatment.—Reports on the ineffectiveness of enterogastrone in the treatment of ulcer continue to appear in the literature. Wollum & Pollard (126) found neither the clinical course nor the secretory or motor patterns significantly altered, and Bone *et al.* (127) found no difference between one group treated with enterogastrone and another group receiving a placebo.

An anion exchange resin (Amberlite IR-100) which reduces acidity and inhibits pepsin activity was reported to hasten markedly the "healing time" compared with aluminum hydroxide [Hall & Hornisher (128)]. Only extensive clinical trial and experimental study will determine the true value of compounds of this type. In the fourth and fifth of a series of articles, Necheles *et al.* (129) presented the chemical and laboratory work, and Bralow *et al.* (130) presented the clinical evaluation of a new antacid (sodium carboxymethyl cellulose) which they believe to be superior to all others. In what seems to be an inconclusive and poorly controlled clinical investigation, Lazarus *et al.* (131) claimed that the administration of protein hydrolysate and dextrin over periods of several weeks caused a significant lowering of fasting gastric acidity. When administered every hour this mixture does appear to be a good antacid provided that it does not leave the stomach too fast (132). Ojha & Venkatachalam (133) reported that large doses of Stilbestrol (α , α' -diethyl-4,4'-stilbenediol; diethylstilbestrol) administered to six male ulcer patients caused prompt relief of symptoms and a decrease in total and free acid in all. The observation is interesting in view of the sex difference in the incidence of ulcer, but because of the large psychogenic factor in the treatment of ulcer, the number of cases is insufficient to draw definite conclusions. These clinical findings are strengthened, however, by the experimental studies of Ojha & Wood (133a) who found that large doses of Stilbestrol given to cats for from 6 to 15 days completely inhibited the acid response to histamine. They suggest that the result may be due to a direct action on the parietal cells.

Miscellaneous.—"Peptic ulcer is increasing in frequency." "Patients with peptic ulcer show certain psychodynamic traits and there is a peptic ulcer personality." "Peptic ulcer is a disease of civilization." In a provocative study Kahn & Freyhan (134) claim that there is insufficient factual evidence to conclusively prove or disprove these oft repeated assertions. Only the greater incidence in males appears definite.

From an analysis of 963 cases of sympathectomy, Hightower, Morlock & Craig (135) and Craig *et al.* (136) presented evidence that this procedure does not alter the course of peptic ulcer nor does it appear to be a causative factor. Ross & Brolsma (137) in an analysis of 214 cases likewise found that thoracolumbar splanchnicectomy does not increase the incidence of ulcer or biliary tract disease. These studies are striking evidence against the theory that the sympathetic system exerts a tonic inhibiting influence on gastric acid secretion.

That disturbances in gastrointestinal mobility are a part of the ulcer syndrome or that constipation is a part of the "vegetative dysfunction" which causes ulcer is a common belief, but Littman & Ivy (138) showed that antacid therapy is the cause in most instances. In agreement with previous work, Baumel, Lazerges & Pedoussant (139) found the blood histamine elevated in active cases of peptic ulcer. Certain phases of protein and amino acid metabolism in gastrointestinal disease and peptic ulcer have been investigated by two groups of workers (140, 141, 142).

When the duodenum is removed from the "gastrointestinal stream" so that it lacks direct mechanical and chemical stimulation, its secretions drop to a low level; consequently, when a duodenal pouch is drained into the stomach by a small end-to-side anastomosis, the secretions are not sufficient to cause definite lowering of gastric acidity or to prevent ulcer in the jejunum in a Mann-Williamson preparation (263, 264). This fact was ignored by Aylett (143) who described a new operation for peptic ulcer. It is predicted that jejunal ulcer will nearly always follow when this operation is performed.

Butler & Capper (144) made a beautiful clinical study of the cause of the postgastrectomy syndrome. They showed that there are two components to the syndrome: first, a sensation of central abdominal fullness and, second, a vasomotor component consisting of a feeling of warmth, sweating, tachycardia, and palpitation. The first component is due to jejunal distension while the second is due to drag on the gastric remnant caused by the weight of the meal and the contents of the afferent loop. The symptoms were abolished by splanchnic block which suggests that the afferent impulses travel in the sympathetic rather than the vagus nerve. Blood-sugar level was not a factor.

PANCREAS

Secretion.—Wang & Grossman (145) used a subcutaneously autotransplanted portion of pancreas to study secretin and pancreozymin stimulation when various substances were introduced into the intestine. The volume of juice was considered the index of secretin and enzyme content of pancreozymin stimulation. Hydrochloric acid (0.5 per cent) caused marked secretin release but a low pancreozymin release. Products of protein digestion (peptone and amino acids) caused marked release of both secretin and pancreozymin. Soap and fats were both good stimulants, soap being second to the protein digestion products in causing release of enzymes. Carbohydrates caused no stimulation. The authors believed that these studies indicate that hormones play a dominant role in the control of pancreatic activity, vagal impulses for the release of enzymes being secondary. They found that atropine caused no inhibition of the stimulating effect of the protein products thus suggesting that cholinergic factors are not involved. Annis & Hallenbeck (146), however, found that Banthine, which has atropine-like actions, caused a definite decrease in the pancreatic response to a meat meal but not of the response to secretin or hydrochloric acid in the duodenum. Kyle *et al.* (147) found that the parasympathomimetic drug Urecholine stimulates pancreatic secretion as well as bile and gastric juice. Dreiling & Hollander (148) made a statistical analysis of the response to secretin in 172 patients without pancreatic disease. Since clinical medicine is particularly concerned with diminished function as evidence of pancreatic disease, they gave particular emphasis to the establishment of the normal minimal values for the volume, bicarbonate concentration, and amylase units. Correction for body weight decreased the scattering of the data. Of the three factors studied, bicarbonate content was the most constant, the mean value being 108 m. eq. per l. Friedman & Snape (149) found that, in pancreatic disease, there may be a dissociation

in the secretion of bicarbonate and enzymes suggesting that they are secreted by different cellular units or that disease may cause selective damage to the dual secretory functions. Hallenbeck *et al.* (150) found no detectable histamine in canine pancreatic juice evoked by several different stimuli. Gross *et al.* (151) found normal pancreatic function in nine cases of primary parenchymatous hepatic disease in spite of the fact that six cases showed steatorrhea. Doubilet & Mulholland (152) described a technique for intubation in humans whereby pure pancreatic juice can be obtained. Miller & Ginsberg (153) made miscellaneous observations on various factors influencing the rate of flow in a patient with an external pancreatic fistula. Colwell (154) described, in rats, the well-known effects of continued loss of pancreatic juice and noted that such loss does not result in fat accumulation in the liver.

Enzymes.—Bernfeld *et al.* (155) found that the properties of human pancreatic and salivary α -amylase were identical but differed from the enzyme from hog pancreas thus showing that it is the species and not the organ which determines the structure. Hokin (156, 157) studied the *in vitro* synthesis of amylase in slices of pigeon pancreas. Glotzer & Seligman (158) found that the serum lipase in dogs decreased markedly following pancreatectomy and remained low for several weeks, after which it began to increase. The unknown source of the extra pancreatic lipase was not influenced by physostigmine or mechohyl. Wirts & Snape (159) presented evidence that Urecholine increased the level of blood amylase by simultaneously constricting the ampulla and stimulating enzyme production. Gross *et al.* (160) found that codeine caused elevation of serum amylase and lipase which might be evident for as long as 24 hr.; spasm of the sphincter of Oddi was believed to be the basic cause. Lopusniak & Bachus (161) found no elevation of serum enzymes following secretin injections in normal subjects but found an increase in certain types of pancreatic disease. Howell & Bergh (162) noted that during cholangiography, when there was evidence of regurgitation of contrast medium into the pancreatic duct, there was a rise in serum amylase. They believe this is due to bile mixed with the contrast medium.

Miscellaneous.—Bliss, Burch, Martin & Zollinger (163) buried electrodes in the human pancreas at operations for biliary disease. On the second and third postoperative days, the head, body, and tail were stimulated and the pain localized by the patient; later by unilateral splanchnic block they determined the afferent pathways involved. Dragstedt *et al.* (164) presented further evidence for the presence of a heat-stable substance in pancreas (lipocaine) capable of preventing fatty infiltration of the liver in dogs after pancreatectomy or duct ligation. Popper & Necheles (165) described a simple method for producing experimental fat necrosis which they state is successful in most cases. Lipp & Hubbard (166) investigated the cause of the low serum calcium in acute pancreatitis and concluded that it is due to the combination of calcium with the fatty acids from the split fats. Lombroso & Dacha (167) reported the interesting observation that depancreatized dogs eliminate from 56.5 to 111.8 per cent of the fat in an olive oil emulsion given

intravenously while normal dogs tolerated the fat well and did not show steatorrhea. An excellent monograph by Thomas on the external secretion of the pancreas appeared during the period covered by this review (168).

GALL BLADDER AND BILE DUCTS

The highly irritating properties of bile were well illustrated in the experimental studies of Sedgwick (169) and of Douglass *et al.* (170). In an experimental study on dogs, Sinkaio & Necheles (171) showed that various experimental procedures, most of which would be classed as "alarming stimuli," may produce gross evidence suggesting extensive gall bladder pathology, but histological examination showed the structure to be normal. Hamre (172) found that vitamin A deficiency in rats caused metaplasia of the epithelium of the bile ducts with obstructive jaundice and dilatation. Dreiling & Lipsay (173), in a study of 327 cases of normal and diseased biliary systems, showed that the biliary pigment response in duodenal contents following secretin injection may give important information on the condition of the biliary tract. Curreri & Gale (174) reported a beautiful study on common duct pressures in human subjects. They showed that various physiologic activities, walking, talking, and straining increased intraductal pressure and that the pressure ordinarily required to overcome the tone of the sphincter of Oddi causes neither pain nor discomfort. Certain analgesics and parasympathomimetic drugs (Urecholine) may increase the sphincter tone to a point where ductal pressure will rise to the painful level. This pressure was found to be 20 cm. or more of water. Atropine, several antispasmodics, and a fatty meal all failed to lower ductal pressure. In one patient following splanchnic block, the ductal pressure was raised to 40 cm. without pain, whereas, next day a pressure of 18 cm. caused severe pain.

INTESTINE

Motility.—Conard (175) studied the immediate effects of x-irradiation on intestinal motility. The latent period of the motor response was very short and the effect appeared to be due to stimulation of cholinergic nerve elements in the intestine directly, without general systemic participation. Andersson *et al.* (176) showed that stimulation of the superior laryngeal nerve caused increased tone or peristalsis which was abolished by section of the vagi. Klinge (177) studied the motility of isolated intestinal segments deprived of one or both of the intrinsic plexuses. Streeten & Williams (178) studied the influence of intraluminal pressure on the passage of fluid through Thiry-Villa loops in dogs. A detailed study of the action of epinephrine on guinea pig intestine was made by Munro (179). Faik *et al.* (180) found that vagotomy did not produce marked effects on intestinal motility but presented a detailed study of what effects were noted.

The studies of Chapman *et al.* (181), Rowlands *et al.* (182) and Posey & Bergen (183) on intestinal motility in man are of great physiological interest.

The studies of Henrikson (184), Craver & Barrett (185), Streeten (186), and Gazes *et al.* (187) deal with the influence of inorganic constituents on intestinal motility and reactivity. Lepore *et al.* (188) studied the effectiveness of Bantline as a depressor of intestinal motility in patients with diarrhea. Szasz (189) presented a theoretical discussion of physiologic and psychodynamic mechanisms in constipation and diarrhea.

Absorption.—Cook & Thomson made a comparative study of fat absorption in the rat, guinea pig, and rabbit (190). Reiser & Bryson (191) using rats showed that free fatty acids and triglycerides are absorbed by the same route. Bollman *et al.* (192) studied the lipids in intestinal, thoracic duct, and liver lymph following fat feeding. When the neutral fat concentration of thoracic duct or intestinal lymph was at its peak, there was a threefold increase in phospholipid content which suggests that the mucosa of the small intestine is a source of plasma phospholipid, at least during fat absorption. Berry & Ivy (193) found no evidence of intestinal absorption of mineral oil by dogs even when the particle size was very fine (0.2 to 0.5 μ), a finding which is not in agreement with the partition hypothesis of fat absorption; however, in premature infants reducing the particle size greatly increased the amount of fat absorbed [Morales *et al.* (194)]. Morales *et al.* (195) also found that when premature infants are placed on low or high fat diets, the percentage absorbed remains about the same. Bergstrom *et al.* (196) studied the mechanism of fat absorption using stearic acid labeled with C¹⁴ and mixed with other fats. Froelich (197) studied the plasma lipids in normal subjects and patients with fatty diarrheas after administration of a fatty test meal. Gibson & Wiseman (198) studied the rate of disappearance of the D and L forms of 13 amino acids from isolated intestinal loops in rats. In each instance the L isomer disappeared faster; they regard this as evidence for an active selective process in amino acid absorption. Feinstein & Smith (199) found that protein digestion was not impaired in premature infants as judged by nitrogen absorption when casein or casein hydrolysate was fed with the basic diet. Bogdanove & Barker (200) found that phlorhizin inhibited the absorption of glucose, galactose, and possibly of mannose and sorbose, but not of fructose. They suggested that this may indicate the presence in rats' intestinal mucosa of a specific enzyme for phosphorylation of fructose. Vidal-Sivilla (201) found that glucose absorption was greater from isotonic than from hypotonic mixtures. Mann & Koler (202) administered crystalline urobilinogen to rats parenterally or orally. In the former instance, about 75 per cent appeared in the bile and variable but smaller amounts in the urine and there was no evidence of conversion to bilirubin; by the latter route only a very small amount appeared in the bile suggesting little intestinal absorption. Gabrio & Salomon (203) found that ferretin was involved in the absorption of iron from the equine intestine and that the lymphatic system also played a role.

Digestion and absorption were studied on four human subjects in which all but approximately 2 ft. of small intestine had been resected and the re-

maining portion anastomosed to the large intestine (204 to 206). Althausen *et al.* (204) studied two of the cases and found that the absorptive capacity of the intestinal remnant increased markedly during the period of study. Absorption of glucose and water began increasing first and was soon normal. Absorption of amino acids and methionine followed and returned to practically normal levels. Fat absorption returned to normal as judged by the butter absorption test but not by the vitamin A absorption test. They believe that following massive resection of the small intestine four types of adaptation occur: (a) adjustment in body weight, (b), functional increase in absorptive capacity, (c) anatomical expansion of the remaining absorptive surface, and (d) assumption by the colon of some of the functions of the small intestine. Bean *et al.* (207) compared the concentration of various absorbed substances in systemic venous blood with that in venous blood from large portal anastomatic veins in patients with cirrhosis of the liver.

Miscellaneous.—The effect of anoxia on various phases of intestinal activity was reported by West, Hadden & Farah (208), Furchgott & Shorr (209), and Van Liere *et al.* (210). On the basis of their studies the last mentioned workers conclude that the effect of hypoxia on the propulsive movement of the small intestine could be used as a criterion for acclimatization. Fisher & Parsons (211) derived a new expression relating mucosal surface area to linear measurements of transverse and longitudinal sections of intestine which they state is applicable to any species. In the rat they found that glucose absorption is nearly exactly proportional to mucosal surface and that glucose absorption per unit of mucosal surface increases from the ileocecal valve upward. This expression may prove very valuable in metabolic and absorption studies. Quastler *et al.* (212) studied acute intestinal radiation death in mice. They found that a survival time of $3\frac{1}{2}$ days was constant over a wide range of dosage and that in order to elicit this standard time of death it was only necessary to radiate any large portion of the intestine. Wierda (213) attempted to determine whether different diets would alter the work of the intestine and cause hypertrophy as in other organs. The results are interesting but not altogether clear. Cook *et al.* (214) reported five cases of severe bulbar poliomyelitis with gastrointestinal perforation, hemorrhage, or both, and speculated on the possibility that these were due to midbrain damage as emphasized by Cushing. It would appear that they might just as well be nonspecific and a part of the alarm reaction which would surely occur in severe bulbar poliomyelitis. Merten *et al.* (215) studied enzymatic disturbances in the gastrointestinal tract and described their method for determining the gastric proteolytic enzyme cathepsin. Martin (216) studied the distribution of alkaline phosphatase in the intestine of several species and noted that there is a relationship between it and the development of the striated border. The secretions of the gastrointestinal tract contain potassium in a concentration equal to or greater than plasma; hence, continued loss of gastrointestinal secretions would soon lead to potassium depletion. This syndrome has been studied clinically (217) and experimentally (218).

COLON

There is still considerable uncertainty regarding the vagal innervation of the colon, but prevailing anatomical belief is that vagal fibers do not go below the splenic flexure. The favorable results obtained by vagotomy in the treatment of ulcerative colitis and regional enteritis (219, 220), however, suggest that vagal innervation may extend to the rectosigmoid junction or below. Schlitt, McNally & Hinton (221) studied the problem of colon innervation in dogs. One balloon was placed just above the internal anal sphincter and another still higher. The basic motility and the reaction to pain were studied. In normal dogs, there was an increase in tone and contractile activity in response to pain. Bilateral sacral parasympathectomy was then performed. Following the operation there was great difficulty in defecation and urination but no change in basic motility or the response to pain. In a second series it was found that bilateral thoracic vagotomy likewise failed to alter basic motility or response to pain. In a third group both sympathetic and parasympathetic nerves were cut. In these there was less difficulty in defecation and urination, but the basic motility became hyperactive and bizarre, reaction to pain was greatly altered in that after a latent period of 2 min. there was either a period of greatly increased tone or the passage of large and prolonged peristaltic waves. These activities lasted for as long as 10 min. These reactions of the denervated colon to pain suggest the possibility of a humoral factor acting on the sensitized colon.

Most clinicians agree that mucus colitis and the "irritable colon" are psychosomatic disorders (222), and evidence is beginning to accumulate which suggests that chronic ulcerative colitis may also be largely psychogenic (223). Almy (224) studied the reactions of the colon to pain and emotional stress in normal subjects and patients with an "irritable colon" and found that both might show marked changes in motility (either increase or decrease), as well as engorgement during periods of tension. It is easy to believe that constant repetition of these responses could, over years, lead to either functional or organic disease. Kern, Almy & Stolk (225) found that Banthine was very efficient in counteracting most factors (food, Urecholine, morphine) which increase colonic hypermotility but that it only partially inhibited the hypermotility produced by emotional stress. Lake *et al.* (226) found no evidence supporting the hypothesis that pancreatic secretions play an etiological role in ulcerative colitis. Studies on the general metabolic derangements (227) and amino acid excretion (228) in ulcerative colitis have been reported. Berger, Quinn & Homer (229) studied the effect of desoxycorticosterone on the colon and found that it acts here, as elsewhere, to cause reabsorption of sodium. Hiatt (230) studied the altered physiology in congenital megacolon, and Fawcett (231) presented some interesting experiments planned to elucidate the pathogenesis of the condition. He found that partial obstruction of the bowel in young animals leads to marked dilatation, while in adult animals, the result is hypertrophy.

RECTUM

Schumacher & Guthrie (232) showed that distension of the rectum caused a rise in arterial pressure which might be very marked. This, by stretching the pain sensitive intracranial arteries, caused headache which could be relieved by bilateral pressure on the carotid arteries, increasing the intracranial pressure or giving tetraethylammonium chloride. Goligher & Hughes (233) showed that distension of the bowel up to 15 cm. above the anal orifice caused a sensation of fullness in the rectum and a desire to defecate, while distension above this level caused a purely abdominal sensation in the suprapubic or left iliac region simulating abdominal cramp. By anesthetic block or operative division, it was shown that the former sensation was mediated by the parasympathetic and the latter by the sympathetic nerve supply. Einsel & Einsel (234) studied two patients in whom the rectosigmoid had been resected and found that distension of the rectal stump resulted in evacuation of the colon through the colostomy opening thus showing the reflex nature of the initiation of defecation. Rubin *et al.* (235) showed that bacterial activity in the feces does not influence rectal temperature.

VOMITING

Wang & Borison (236) showed that the emetic effect of copper sulfate in dogs can be very accurately standardized as to dose and latent period. Vagotomy alone almost doubled the dose required and the latent period of the response, while sympathectomy caused no change. Vagotomy plus sympathectomy caused an eightfold increase in the dose required and greatly prolonged the latent period. Borison & Wang (237) reported that in dogs there is a chemoreceptor trigger zone for emesis quite distinct from the vomiting center. Bilateral destruction of this trigger zone resulted in dogs which were permanently refractory to apomorphine by vein but which vomited when copper sulfate was given orally. They state that the demonstration of the trigger zone for emesis is "the first such discrete and specialized chemoreceptor area demonstrated to reside within the central nervous system." Borison & Brizzee (238) described the morphology of this chemoreceptor trigger zone in cats; it is a nonneural zone having the morphologic characteristics of chemoreceptors elsewhere. Rubin & Metz-Rubin (239), contrary to the experience of others, reported that Dramamine (dimenhydrinate) caused a significant decrease in the incidence and severity of postoperative nausea and vomiting.

LYSOZYME

The mucolytic enzyme lysozyme, which has been incriminated as a causative agent in peptic ulcer and ulcerative colitis, has been extensively investigated. In two excellent papers, Gray *et al.* (240) and Reifenstein *et al.* (241) studied lysozyme in relation to peptic ulcer. They found that the lysozyme content of the gastric juice from patients with duodenal and

gastric ulcer does not exceed normals. Under histamine or insulin stimulation, the total output and concentration of lysozyme varied directly with the gastric mucoprotease and indirectly with that of mucoprotein; hence, they concluded that lysozyme originates from the surface epithelial cells. Their evidence led them to conclude that lysozyme reflects the tissue response to injury and that it does not play a significant role in etiology. In ulcerative colitis, Gray *et al.* (242) found high lysozyme titers which decreased in remissions and increased in exacerbations. Oral administration of a detergent, Aerosol OT (di-octyl sodium sulfosuccinate) produced a marked fall in fecal lysozyme titer but prolonged administration to patients with ulcerative colitis did not alter the course of the disease or produce remissions.

Nickel, Gordon & Andrus (243) made daily instillations of dissolved lysozyme crystals alone, or in combination with the ileostomy drainage from patients with ulcerative colitis, into isolated loops of canine colon but were unable to produce more than transient inflammation and superficial erosion. Moeller, Marshall & Kirsner (244) and Marshall *et al.* (245) found that the lysozyme content of the washings from the rectums of dogs was increased following cauterization of the mucosa and in the bloody diarrheal stools produced by chronic stimulation with mecholyl. From these facts they concluded that the rise in lysozyme titer in ulcerative alimentary disease is a result rather than a cause of the ulceration.

PITUITARY AND ADRENAL HORMONES

The excellent studies of Gray *et al.* (246) and Spiro *et al.* (247) showed that adrenocorticotrophic hormone, acting by way of the adrenal gland, stimulates the secretion of gastric pepsin and uropepsin. Davenport & Chavre (248) found that the adrenal hormones have no effect upon acid secretion by the *in vitro* mouse stomach preparation. Smyth (249) stated that adrenocorticotrophic hormone administration may be dangerous in peptic ulcer because of its stimulating effect on gastric pepsin and its inhibitory effect on the growth of granulation tissue. Alrich *et al.* (250) showed that adrenocorticotrophic hormone and cortisone delay the healing of wounds by retarding the production of the mesenchymal cellular elements of repair. Sandweiss *et al.* (251) reported that adrenocorticotrophic hormone and cortisone caused treated Mann-Williamson dogs to survive at least twice as long as controls. An extract from pregnant mares' urine caused phenomenal survivals of 6, 8, and 10 months. Their reports on human ulcer patients are not convincing.

Cortisone and adrenocorticotrophic hormone have been reported to cause remission and subjective improvement in ulcerative colitis and regional enteritis (252, 253), but objective improvement is usually lacking (254 to 256). From the evidence available it appears that these hormones do not specifically effect the large intestine in these conditions. Hardy (257) claimed a relationship between adrenal cortical function, urinary volume, and the volume of gastrointestinal secretions following colon resection. Schwartz-Teine (258) claimed that certain clinical and metabolic findings in celiac disease suggest adrenal cortical insufficiency.

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FUNDAMENTALS OF BLOOD CLOTTING

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This review covers the interval between July 1, 1949, and June 30, 1951. Obviously, space limitations preclude a complete citation of every paper. The older literature is cited when required for clarity or readability. For collateral reading, the excellent review of Astrup (1) is recommended. Likewise of particular interest are the series of the Transactions of the Conferences on Blood Clotting and Allied Problems (2, 3, 4, 5), which include unembellished discussions of many subjects covered in this review.

The blood clotting literature can be divided into three parts: fundamental aspects, anticoagulation therapy, and hemostasis. The fundamental aspects are emphasized in this review. The book by Marple & Wright (6) is available for those interested in anticoagulation therapy. A recent book by Quick (7) covers the problem of hemostasis. A review by Koller (8) summarizes some of the papers not cited in this article.

Prior to 1943, many investigators believed that all essential factors required for blood clotting were included in the classical theory which held that the formation of thrombin results from the interaction of thromboplastin, calcium, and prothrombin. It is now clearly demonstrated that at least one or two more factors are involved in the mechanism of thrombin formation. One of these factors is variously termed thrombogen (9, 10), prothrombin A or labile factor (11, 12), plasmakinin (13, 14), prothrombin accelerator (15), factor V (16) (i.e., the fifth factor in blood clotting), proaccelerin (17), accelerin (1), and accelerator globulin (18).

The consensus of most workers is that all of the previously named factors are one and the same. In addition, a number of investigators believe that still other factors exist. For descriptive purposes, the new factors are distinguishable from the classical ones by the qualifying term "accessory." This term does not imply that they possess merely a supplementary action to the classical factors; indeed, they may be as necessary as prothrombin.

ACCESSORY FACTORS

Factor V.—For the purpose of this review the term "factor V" is used. We know that this will not be universally pleasing. The adequacy of the term "accelerin" or "accelerator globulin" depends somewhat on whether the factor acts stoichiometrically or catalytically. If the former obtains, then it is absurd to designate one component as an accelerator or a converter, and

¹ Originally, Quick designated the labile factor as component A (11), but he now uses the latter term to refer to the classical prothrombin of the earlier writers (90).

the other component as the agent acted upon. This is analogous to saying chloride accelerates the conversion of sodium into salt. The term "labile factor" is objectionable since it is labile only under certain conditions and for certain species. Historically, Nolf's "thrombogen" has precedence, but this term is not widely used.

Owren (16) showed that factor V is a globulin, thermolabile (58°C. for 30 minutes), and nondialyzable through a cellophane membrane. It precipitates maximally with 33 to 50 per cent ammonium sulfate, and from solution at pH 5.0 to 5.5 when freed of salt by dialysis.

All workers agree that factor V affects the first stage of clotting by aiding the conversion of prothrombin to thrombin, but there is a notable lack of unanimity as to whether factor V acts catalytically or through direct permanent union. Indeed, the literature seems to contain divergent and mutually contradictory observations on the role of factor V in the conversion of prothrombin. It appears to the reviewers that under certain artificial conditions, thrombin can be formed in the virtual absence of factor V, but under more physiological conditions, factor V becomes necessary.

The first worker to subscribe to a stoichiometric theory was Owren (19). He believes that during the formation of thrombin, factor V is consumed but thromboplastin is not. He finds that in the presence of an optimal amount of thromboplastin, the degree of conversion of prothrombin to thrombin varies with the amount of factor V. Furthermore, with suboptimal amounts of thromboplastin, but optimal amounts of factor V, the reaction rate is slow, but eventually all prothrombin is converted. This is strong evidence for the consumption of factor V. What makes Owren's experiments particularly impressive is that each of the reagents he uses for these experiments is thoroughly freed of all of the other clotting reagents, a meticulousness seldom encountered among investigators in the field of blood clotting. Owren is by no means alone in his opinion concerning the utilization of factor V in the formation of thrombin. Lewis & Ferguson (20) use purified prothrombin and accelerator globulin (both obtained from Seegers), and report that the quantity of thrombin formed, when these reagents are mixed with Ca^{++} and thromboplastin, is dependent upon the quantity of each reagent in the original mixture. If factor V possesses only a catalytic role in the conversion of prothrombin, one would expect that changes in the concentration of factor V would influence the length of time required for a given amount of prothrombin to be converted. However, in Lewis & Ferguson's experiment, the total amount of thrombin formed is dependent upon the amount of factor V present. This suggests a noncatalytic reaction.

Quick & Stefanini (21, 22) also agree with Owren (19) and with Lewis & Ferguson (20). They state that very little prothrombin (i.e., what they now call component A¹) is consumed when plasma clots, provided the plasma is deficient in factor V. Even an excess of thromboplastin and calcium causes very little increase in the consumption of prothrombin in the deficient plasma. In fact, Quick (11) believes that the labile factor (factor V) consti-

tutes an integral part of the prothrombin moiety. Stefanini & Crosby (23) report that the prothrombin level and factor V content of the serum are roughly parallel—the more prothrombin consumed, the less factor V remains. Honorato *et al.* (24) make a similar observation. Alexander *et al.* (25, 26) stress the point that the factor V content of serum is lower than plasma. Furthermore, if serum is prepared by addition of thromboplastin to the blood, the loss of factor V is more striking. Serum prepared from hypoprothrombinemic plasma has a higher content of factor V than normal serum. They believe that these observations indicate that factor V is not a catalyst.

Seegers (27), Seegers & McClaughry (28), and McClaughry & Seegers (29) disagree that factor V is a necessary reagent for the *in vitro* conversion of prothrombin to thrombin. They believe that prothrombin contains within itself all the necessary components for thrombin formation. They exclude not only factor V, but also stress the unessentiality of Ca^{++} and thromboplastin. This conclusion is based on the observation that purified prothrombin dissolved in 0.72 *M* sodium citrate solution is slowly activated to thrombin. This seems to be strong evidence against the stoichiometric role of factor V, provided, of course, the purified prothrombin used in these experiments was completely free of the last traces of factor V and thromboplastin.

Flynn & Standley (30) also find the factor V content of human serum to be considerably reduced when blood clots spontaneously. No appreciable utilization of factor V occurs, however, if the blood clots in the presence of an equal volume of isotonic calcium chloride (0.11 *M*). It seems to us that the experiments of Seegers *et al.* and Flynn *et al.* indicate that factor V may not always be an indispensable reagent in the conversion of prothrombin to thrombin, since, in the presence of a highly artificial medium such as 0.11 *M* calcium chloride or 0.72 *M* sodium citrate, prothrombin apparently can be converted to thrombin with little utilization of factor V. Nevertheless, the evidence does favor the viewpoint that, under physiological conditions, factor V is utilized in the conversion of prothrombin to thrombin.

A number of procedures are available for assaying factor V. Both two stage (31, 32) and one stage prothrombin assays (33) have been modified for this purpose. In the two stage modification a constant amount of prothrombin, poor in factor V, is converted to thrombin by adding it to test amounts of factor V, together with an optimal amount of calcium and thromboplastin (i.e., first part of the two stage method). The amount of thrombin formed in this mixture is then determined by adding an aliquot of the reaction mixture to standardized fibrinogen solution (i.e., second part of the two stage technique) and noting the clotting time. By removing an aliquot every few minutes until the maximum thrombin titer has been obtained, one can determine the effect of the test substance on the speed of thrombin formation and the extent to which the reaction has gone to completion, both factors being influenced by the amount of factor V added.

In the one stage method, the test substance is added to plasma deficient in factor V. After adding optimal amounts of calcium and thromboplastin

to the substrate, the clotting time of the mixture is accepted as a measure of the amount of factor V added. It is obvious that the one stage method lacks the versatility of the two stage method since the maximum thrombin titer cannot be measured, owing to the fact that much of the prothrombin continues to be converted to thrombin after the end-point of the test has been reached. One stage methods include those of Owren (34), Quick & Stefanini (35), Stefanini (36), and Fantl & Everard (187). Two stage methods include those of Owren (37), Ware & Seegers (38), Flynn & Standley (30) and Carter & Warner (39, 40). The Stefanini test (36) has the merit of simplicity and from our own experience is satisfactory for routine clinical studies. For more analytical work, the two stage method is preferable.

Other accessory factors.—The evidence for accessory factors other than factor V is more tenuous. Indeed, this aspect of blood clotting is the most difficult to evaluate. Part of the difficulty is related to the use of different assay procedures. In addition, there is the added complication that various species seem to react differently, making it hazardous to generalize. In most cases, the existence of a new factor is postulated from data showing a clot-accelerating effect of serum, or a faster conversion rate of prothrombin. The question remains whether the accelerating effect is really due to a distinct factor, or whether it can be explained on the basis of reagents contaminated with traces of partly activated prothrombin or thrombin. If there is a new factor, is it normally present in the circulating blood, or is it evolved from an inactive precursor? Could it represent an activated complex of several known factors? Although none of these questions can be answered definitely, we think there is value in reviewing the work that has been done.

The concept of accelerator factors is not new. Owren (16) and Astrup (1) cite the older literature which hints strongly at the role of accessory factors in the clot-accelerating effect of serum. Much of Owren's monograph (16) deals with his investigations of a factor which he calls factor VI. Owren mixes solutions of purified prothrombin, thromboplastin, and factor V, then adds calcium chloride. As would be expected, a certain amount of thrombin is formed, as judged by the ability of the mixture to cause clotting of purified fibrinogen. He finds that such a mixture also contains a new component which apparently appears while the thrombin is forming. This factor may represent an intermediate in the formation of thrombin, somewhat analogous to Ferguson's "unripe thrombin" (41). On the other hand it may be a "convertibility factor" as originally postulated by the Iowa workers (42, 43) and produced in some obscure way as a side reaction.

A recent paper by Koller *et al.* (44) hints that another component, factor VII, is needed for the full maturation of factor VI. Nevertheless, it is still not clear how factor VI is formed. Owren believes that factor V is an integral part of factor VI, "entirely or partly." Ware *et al.* (45) and Murphy *et al.* (46) are in essential agreement with the derivation of such a factor from factor V. They find that a factor V preparation made from plasma has less activity than one prepared from serum. Accordingly, they designate one

component as plasma accelerator globulin (Owren's factor V) and the other as serum accelerator globulin [Owren's factor VI (?), Koller's factor VII (?)]. They believe that thrombin plays the key role in the formation of the serum factor.

Carter & Warner (47) advance an alternate hypothesis which explains the increased activity of serum without postulating the existence of factor VI. They suggest that in serum, more factor V is available than in plasma. They believe that fibrinogen envelops the factor V "molecules," forming a complex which makes it less available to react during prothrombin conversion. However, when fibrinogen is converted to fibrin by the addition of thrombin, factor V becomes more available. Consistent with this hypothesis is the observation that a decrease in factor V occurs when fibrinogen is added back to the defibrinated plasma.

Jacox & Bays (48) and Jacox (49) also describe a factor which they designate as "serum prothrombin converting factor." They observe that a mixture of serum and thromboplastin incubated for 1 min. will then clot oxalated plasma within 8 to 12 sec., but will not clot deprothrombinized plasma or fibrinogen solution. With longer periods of incubation, the clot-producing quality of the mixture becomes progressively lessened. As the authors point out, these experiments are reminiscent of those done by Owren in demonstrating factor VI.

Other factors have been described by de Vries *et al.* (50), Alexander & Landwehr (51), Mann (52), and Milstone (53). The stability of these factors suggests that they are not the same as factor VI, but are perhaps factor VII. Alexander and his co-workers (50, 51) designate their factor as the serum prothrombin conversion accelerator (SPCA). They believe that this factor is evolved from an inactive plasma precursor during clotting and that factor V is utilized in its formation. Furthermore, they attempt (54) to correlate SPCA with serum accelerator globulin. They report that an analysis of a sample of serum accelerator globulin obtained from Seegers showed it to contain both labile and stable factors. They believe that the former is factor V and the latter is their SPCA. They disagree with Seeger's interpretation that thrombin converts plasma accelerator globulin into serum accelerator globulin, and advance an alternate hypothesis that thrombin converts a precursor of SPCA into the active form. They have partially purified SPCA (54). These workers also report (55, 56, 57) that the amount of SPCA evolved varies inversely with the residual prothrombin in serum. Recently, Alexander *et al.* (58) report a patient with a congenital deficiency of the plasma precursor of SPCA.

Mann (52) and Mann & Hurn (59), using a modified two stage prothrombin assay, find that preliminary mixing of the thromboplastin with dilute serum or plasma causes considerable acceleration of the initial rate of thrombin formation, particularly in prothrombin assays on plasma of patients receiving dicumarol. The necessity of the preliminary reaction of the thromboplastin is used by the authors to justify their designation of the serum

principle as the "co-thromboplastin factor." Mann & Hurn purify their factor (59) by adsorbing serum with tricalcium phosphate and eluting with citrate. Milstone (53) also describes a substance which activates prothrombin. This material is prepared from plasma globulin.

Sørbye *et al.* (60, 61) isolate a factor from the plasma of vitamin K deficient chicks which shortens the prothrombin time of dicumarol plasma. They also isolate a factor from dicumarol plasma which decreases the prothrombin time of plasma from vitamin K deficient chicks. They claim that neither of their new factors is factor V and suggest the equivalence of one of them with Alexander's SPCA.

The methods used by Sørbye *et al.* to purify one of their factors have much in common with the methods used to purify co-thromboplastin, SPCA, and Milstone's factor, suggesting that the four factors may be the same, or at least closely related. Furthermore, all workers except Milstone report that their factors are decreased in the plasma of patients receiving dicumarol.

Owen & Bollman (62) point to the well-known fact that the prothrombin conversion rate of plasma varies with the dilution of the latter. They present evidence that slowing of the rate is related to dilution of certain conversion factors in the plasma, rather than dilution of the prothrombin *per se*. This conclusion is supported by the observation that the addition of purified prothrombin to the dilute plasma does not increase the amount of thrombin formed per second.

In contrast to the workers postulating new factors, Quick & Stefanini (21) resurrect Bordet's old concept. They explain the results of Alexander and the others on the theory that prothrombin exists in an inactive or precursor state and an active or free state. They believe that the accelerator effect is due to an increase in the free prothrombin, since, in their opinion, it is only this type of prothrombin which is converted to thrombin. It is fair to say that Stefanini did not long subscribe to the Quick-Stefanini theory. In later papers (this time collaborating with Crosby) Stefanini (63, 64, 65) admits there is an accelerator factor other than prothrombin.

In summary, a vast amount of work from many laboratories all points to the possibility of one or more new factors. What is now needed are more precise methods of assay and continued efforts at further purification of reagents. Eventually, this should permit the blood clotting factors to be recombined and kinetically analyzed in accordance with the standard procedures of reaction mechanics.

CLASSICAL FACTORS

Prothrombin and thrombin.—Up to the present, most laboratory workers and clinicians have avoided the laborious preparation of thrombin by using the commercially available preparations. For a time, both bovine and human thrombin were available, but recently the thrombin made from human plasma has been recalled from the market since its clinical use is reported to have been a source of two epidemics of serum hepatitis (66). In this respect,

the thrombin made from bovine plasma has proved safer; at least we know of no reports of toxicity resulting from its use.

It has long been known that plasma prothrombin can be preferentially adsorbed by a number of reagents such as magnesium hydroxide or tricalcium phosphate. The adsorbed prothrombin can be eluted and converted to thrombin by thromboplastin, factor V, and calcium. However, the thrombin so obtained is frequently unstable, being rapidly inactivated by antithrombin present as a contaminant.

At present, the most successful method of obtaining a stable thrombin in high yield is the one originally devised by Seegers, Brinkhous, Smith & Warner (67) and later amplified by Seegers (68). Originally, the purified prothrombin was converted to thrombin by adding thromboplastin and Ca^{++} , but recently Seegers (27) reports that purified prothrombin in 25 per cent sodium citrate solution is slowly converted to thrombin. Furthermore, 100 per cent yield of thrombin can be obtained by the addition of 3-chloro-4,4'-diaminodiphenyl sulfone (27) or 3-methyl-4,6,4'-triaminodiphenyl sulfone (28) to the prothrombin-citrate mixture. A new method for the production of purified prothrombin is reported by Surgenor *et al.* (69).

Seegers & McClaughry (28) observe that addition of thrombin to a purified prothrombin citrate solution decreases the activity of the prothrombin. McClaughry *et al.* (70) report that purified prothrombin can be dried from the frozen state without immediate loss of activity, but if after drying, it is kept in a desiccator, it eventually shows progressive loss of activity until it becomes completely refractory to Ca^{++} , thromboplastin, and factor V. Curiously, however, the refractory prothrombin can still be converted to thrombin by 25 per cent sodium citrate.

Gollub *et al.* (71) define the "critical absorption level" for prothrombin as the minimum quantity of absorbent required to render plasma incoagulable for 1 hr. at 37°C. after the addition of thromboplastin and Ca^{++} . With human plasma, the critical absorption levels on a dry weight basis per 100 ml. plasma are: 2.0 gm. for barium sulfate, 0.2 gm. for aluminum hydroxide and 0.2 gm. for tricalcium phosphate.

The theory of the one and two stage methods used for prothrombin assays has been outlined under factor V. Modifications of both methods include those by Sandmann (72), Schwager & Jaques (73), Alexander *et al.* (74), Losner *et al.* (75), Owren (76), Shinowara (77), Herz *et al.* (78), Stefanini & Crosby (63), Schultze (79), Rieben (80), Goldfeder *et al.* (81), Frommeyer (82), Koller & Frick (83), Marachy (84), Isenberg (85) Warren & Belko (86), Koller & Wanner (87).

It will be recalled that certain discrepancies exist between the one stage and two stage methods of prothrombin assay. For example, canine plasma gives a much faster Quick prothrombin time than human plasma (6 sec. versus 12 sec.). However, with the two stage method the prothrombin unitage is essentially the same for the two species (300 to 375 units per ml. of plasma). It was thought for a time that differences in the amount of

factor V might explain the discrepancies between the two methods. The addition of factor V to the Quick test, however, does not speed the conversion of human plasma; hence some other explanation must be sought. For years, Quick maintained that this discrepancy is due to the fact that canine plasma has five times as much prothrombin as human plasma. It will also be recalled that the Iowa investigators showed that another explanation (and one more in accord with the facts) is that canine prothrombin converts more rapidly than human prothrombin, causing the thrombin titer to rise faster and thus accounting for the decrease in the clotting time of the Quick test. The Iowa group could not decide from the available evidence whether the rapid conversion of canine prothrombin results from intrinsic or extrinsic factors. More recently Quick, working with Stefanini (21), has modified his original concept. He now believes that prothrombin exists in an active state (i.e., can be converted into thrombin) and inactive state (i.e., cannot be converted into thrombin), and it is only the active form of prothrombin that is responsible for the Quick prothrombin time. Furthermore, he recants his previous dogma that the canine species has five times as much prothrombin as the human. He now makes the point that the total amount of prothrombin is the same in both human and dog, but canine plasma has five times as much active prothrombin as human plasma and it is this large amount of active prothrombin that explains the faster clotting time of the Quick test on canine plasma. This terminological twist is remarkably similar to the original Iowa theory, but the reader is to be reminded that the problem is still unsolved as to whether the faster conversion of canine prothrombin is due to an inherent property of the prothrombin itself or to extrinsic factors which cause it to convert more rapidly.

In the past, much has been written about the relative merits of the one and two stage methods of prothrombin assay, but with the clinical discovery of factor V and the evidence indicating that other factors may exist, it is obvious that these factors must be added in optimal amounts before any assay can be said to be truly a measure of prothrombin. This attitude is best summarized by Smith (88). Sporadically, Quick still maintains that his one stage method measures only prothrombin. However, he and Hussey (89) report that the thromboplastin concentration required for the minimum clotting time in the Quick test varies with the concentration of prothrombin. Even Stefanini (65) deviates by stating that the one stage test is not a specific measure of prothrombin concentration. Quick & Stefanini (90) recently confirmed the observation of others that prothrombin (i.e., component A) may vary between 50 and 100 per cent without affecting the clotting time of the one stage test. Johnston & Ferguson (91) find that the Iowa two stage prothrombin assay has an experimental error of 10 per cent. For an analysis of the Quick one stage test, the report of Tocantins *et al.* (92) is highly recommended.

A number of articles deal with the estimation of prothrombin in serum. With the two stage prothrombin assay on serum, there is a progressive loss

of prothrombin. In 1939, Brinkhous (93) reported that the loss of prothrombin is slower in hemophilic plasma than in normal plasma. Quick (94) has also devised a "prothrombin consumption test" using his one stage method. Curiously, however, the Quick one stage method on hemophilic serum, serum from thrombocytopenic plasma, and even normal serum shows a hyperactive phase during which the clotting time becomes shorter than it was for the original plasma (21, 95, 96). The question arises as to whether this is an intrinsic hyperactivity of prothrombin owing to partial activation, or whether it is the result of an accelerator factor evolved during clotting (factor VI, etc.). Quick's theory that the explanation is due to an increase in active prothrombin is relatively noncommittal. Langdell *et al.* (97) compare the results of the one and two stage prothrombin utilization assays on serum prepared from normal human blood, normal canine blood, and a group of slowly clotting bloods. The last group included hemophilic blood, platelet-poor plasma, and blood collected in silicone-coated containers. The one stage tests all showed a hyperactive phase, but with the slowly clotting bloods this developed more slowly and persisted longer. They suggest that the hyperactive phase with the one stage test is due to evolution of a serum factor which accelerates thrombin formation [factor VI (?), SPCA (?)]. They conclude that this factor is present in adequate amounts in the two stage method of assay. The authors suggest that if the one stage procedure were modified by the addition of the serum accelerator factor, the discrepancies in the serum prothrombin values might disappear. We interpret this to mean that if an accelerator factor, such as SPCA, were routinely added to the Quick one stage test, normal human plasma might clot in much less than 12 sec. Along this same line, Stefanini & Crosby (64) publish a formula by which the prothrombin time of serum can be corrected for serum accelerator activity. When correlated with other tests, both the one and two stage prothrombin utilization assays on serum are of value in the diagnosis of hemophilia.

In a preliminary report, Owren & Bjerkelund (98) state that aged serum contains as much prothrombin as does the plasma from which it came. However, two years have elapsed without publication of the supporting data. Recently Koller *et al.* (44) explain Owren & Bjerkelund's results on the basis of factor VII rather than persistence of prothrombin in the serum.

In another preliminary report, Owren (99) confirms the previous work of Warner & Owen (100), showing that patients with untreated pernicious anemia have a hypoprothrombinemia which is refractory to vitamin K but is correctable by injections of liver extract. The Norwegian workers (99) isolate the factor from crude liver extract which corrects the hypoprothrombinemia, but the details of the method are not given.

It has been known for some time that the effect of vitamin K administration on the hypoprothrombinemia owing to liver disease is variable and depends upon the severity of the liver damage. A number of recent reports confirm this. Most of the recent papers also include investigations

of the factor V level in liver disease. Owren (101) finds that both prothrombin and factor V are reduced in hepatitis, but the fall of prothrombin occurs sooner. Vitamin K has no effect on factor V levels, but does have some effect on the prothrombin levels, depending upon the severity of the liver involvement. Hartmann & Langer (102) also find prothrombin and factor V to be decreased in liver disease. Alexander & Goldstein (103) likewise report a fall of factor V as well as SPCA in severe liver disease.

McCormick & Young (104) confirm the earlier work of Link (105) by their report that aminophylline causes an increase in prothrombin levels. In addition, they also find an increase in factor V. Honorato (106) reports essentially the same observations on rabbits.

It has been recognized for a number of years that a discrepancy exists between the one and two stage prothrombin assays on newborn infants. At birth, the Quick one stage test gives a normal level of prothrombin, but thereafter it decreases progressively until the second or third day. On the other hand, the two stage method shows a 50 per cent level at birth. As yet, this discrepancy is unexplained. A low factor V content of the newborn infant does not explain the low two stage assay since adding an excess of factor V does not give higher values. Likewise, Stefanini reports that the factor V level of newborn infants is normal (107).

Field *et al.* (108) find that the one stage prothrombin time is prolonged in newborn lambs and in newborn pups (the latter finding confirms the previous work of others). Field *et al.* have administered large quantities of vitamin K parenterally to parturient bitches and ewes but this does not change the results of the one stage test. Schultze (79) reports that the foal shows a low plasma prothrombin level but normal factor V content. Schultze (79) finds that immunization of cattle against diphtheria gives a significant decrease of factor V without influencing the level of prothrombin.

Crockett *et al.* (109) publish a case report of a 54-year-old woman who has had abnormal bleeding since the age of two weeks. Two stage assays showed a combined deficiency of prothrombin and factor V. Koller *et al.* (110) describe two new cases of factor V deficiency which caused an abnormal Quick prothrombin time.

Carter *et al.* (111) report the simultaneous effect of acute massive plasmapheresis and chloroform intoxication on prothrombin concentration. They find no evidence of a reserve store of prothrombin. Quick & Collentine (112) have studied the change in prothrombin concentration by giving vitamin K to hypoprothrombinemic dogs. They agree with the rather obvious conclusion of Carter *et al.* that recovery of prothrombin represents an equilibrium between production and utilization. Stefanini & Pisciotto (113) report on the rate of disappearance of injected prothrombin from the circulation of rabbits given dicumarol. They find that 50 per cent of the prothrombin disappears from the circulation in 12 hr., and 80 per cent in 24 hr. Mann *et al.* (114) use hepatectomized dogs to study the rate of disappearance of prothrombin, co-thromboplastin, factor V, and fibrinogen. They present

evidence for a very rapid turnover of prothrombin. The co-thromboplastin decreases more rapidly than prothrombin.

Gerendas *et al.* (115, 116) and Derouaux (117) confirm the older work of Mellanby and others on the effects of intravenous injection of thrombin. This technique still proves to be a useful and effective method of producing temporary afibrinogenemia. Seegers (118) and Boyles *et al.* (119) report that the instability of dilute solutions of thrombin is due to its adsorption on glass.

Calcium.—The role of calcium in blood clotting is still to be elucidated. It is difficult to be certain whether calcium acts catalytically or combines permanently, forming perhaps a cement substance between prothrombin and factor V. Quick (120) champions the stoichiometric viewpoint, and Seegers & Ware (121) support the catalytic theory. Seegers (27) points out that the Quick theory is inconsistent with his experiment in which purified prothrombin is converted to thrombin in the presence of 25 per cent sodium citrate. Mysliveček (122), Milstone (123), and Overman (124) also report the conversion of prothrombin to thrombin in the absence of Ca^{++} .

Quick & Stefanini (125) and Stefanini (126) think that citrate is "anti-prothrombic," for they believe its anticoagulant action to be due to the formation of a complex between prothrombin and citrate, thus preventing the conversion of prothrombin to thrombin. This view is in contrast to the original explanation of Sabbatini, who considered the anticoagulant activity of citrate to be related to its depression of the ionization of calcium. However, in a more elaborate study, Hussey *et al.* (127) present new evidence that citrate does depress the ionization of calcium to some extent. They decalcify citrated plasma by passing it through Amberlite (a cation exchange resin), and find the quantity of calcium removed to vary inversely with the amount of citrate. They reason that if citrate forms a "complex" with prothrombin, then citrated plasma should still yield its ionized calcium to Amberlite. Heparinized blood similarly treated did yield its ionized calcium. De Nicola & Rosti (128) and Honorato *et al.* (129) call attention to an old observation, many times repeated, concerning the importance of the Ca^{++} level in the Quick prothrombin time test.

Thromboplastin.—Thromboplastic activity seems to be an ubiquitous property of tissues and even of secretions, but lung and brain continue to be organs of choice for potent preparations. For many studies it is desirable to have a thromboplastin free of factor V activity. The acetone-dried brain, made according to Quick's directions, has little if any factor V activity, presumably because of the acetone treatment. However, lung extract does contain a variable amount of it, particularly if made from beef lung. In this respect we cite the previous work of Murphy & Seegers (276) who showed that the factor V of beef serum is extremely stable. The contamination of lung extract with a small amount of beef serum probably explains why lung extract seemed originally to be the thromboplastin of choice for the two stage prothrombin assay. We know now that Quick's thromboplastin is

equally satisfactory if factor V is added. McClaughry & Seegers (29) show that, by Chargaff's technique (130), thromboplastin can be made from lung which has very little factor V activity.

The question remains as to whether a thromboplastin or prothromboplastin exists in the circulating blood. Quick (94) believes that a precursor of thromboplastin (i.e., thromboplastinogen) exists, but its presence is deduced mainly by logic, not by experimentation. Hartmann *et al.* (131) also believe that an inactive thromboplastin, distinct from platelets, exists in the circulating blood. Their opinion is based largely on the observation that platelet-poor plasma can be made to coagulate by the addition of crushed glass. In this respect it is to be noted that Tocantins *et al.* (132) use similar evidence for supporting their viewpoint that glass has a strong affinity for a circulating anticoagulant—antithromboplastin. None of Hartmann's evidence negates the Tocantins viewpoint. It will be recalled that Chargaff & West (133) raised the question of a circulating thromboplastin. They found that following high speed centrifugation of normal plasma, the centrifuge cup contained a sedimented pellet which had thromboplastic activity when tested with chicken plasma. Flynn & Standley (134) have repeated these experiments and note that the pellet contains platelets; thus the coagulant activity of the pellet can be readily explained on its platelet content.

It is not yet certain whether thromboplastin acts catalytically or stoichiometrically. Originally Mertz *et al.* (135) reported that thromboplastin was consumed in the conversion of prothrombin to thrombin. Owren (16), however, reinvestigated this problem and showed that the limiting factor is factor V, not thromboplastin. Seegers (27) now agrees with Owren and advances as supplementary evidence the observation that prothrombin can be converted to thrombin in the absence of thromboplastin. Seegers & Ware (121) also confirm Chargaff's observation that thromboplastin used for activating prothrombin and reisolated by high speed centrifugation still possesses activity. Quick continues to adhere to the stoichiometric role of thromboplastin in the formation of thrombin (7).

Horányi (136) investigates the role of euglobulin in coagulation of blood, but the author does not state whether the tonicity of his solutions was controlled, and this makes it difficult to interpret his results. Lewis *et al.* (137) report that fibrinolysin does not inactivate thromboplastin or prothrombin but does inactivate factor V. Halse (138) investigates the activation of the fibrinolytic process by thromboplastin. He believes the lytic action of thromboplastin to be associated with the lipid component and to be relatively nonspecific. Fantl & Fitzpatrick (139) indicate that the fibrinokinase of brain extract is not identical with thromboplastin.

Fibrinogen and fibrin.—A number of physiochemical studies have been done. These include reports by Waugh & Livingstone (140), Shulman & Ferry (141, 142), Hall (143, 144), Porter & Hawn (145), Hunzinger *et al.* (146), Knüchel (147), Wöhlisch (148), Horan *et al.* (149), Bailey *et al.* (150),

Laki (151), and Benkö & Lichtneckert (152). There is a good discussion of this aspect of blood clotting in the fourth Josiah Macy, Jr. Foundation report (153).

Guest & Ware (154) confirm the older observation that thrombin dissolves fibrin. The question can be raised as to whether this unusual activity of thrombin may be related to a contaminant in the thrombin which functions either as a proteolytic enzyme or by the activation of a proteolytic enzyme in the fibrinogen. It seems certain that the proteolytic enzyme is neither fibrinolysin nor trypsin, since it can not be inhibited by antifibrinolysin nor by antitrypsin. Kay (155) also reports that purified thrombin obtained from Seegers is proteolytic to gelatin.

Weiner & Shapiro (156) confirm older work which shows that the normal variation in fibrinogen concentration (180 mg. to 650 mg. per 100 ml. plasma) is not significant in the one stage prothrombin time test, even when the plasma is diluted to 12.5 per cent before doing the Quick test.

Quick & Hussey (157) and Quick (158) reemphasize the old observation, oft repeated, as to the importance of thrombin in clot retraction. They believe that thrombin causes disintegration of the platelets which in turn causes clot retraction. Vroman (159) suggests that the adherence of fibrin to glass is mediated through the platelets and retraction of the clot occurs when the platelets fragment. However, one can question this physical mechanism since Ferguson (160) points out that the adherent clot, formed by the coagulation of platelet-poor plasma, can be made to retract by merely adding platelets.

Shinowara & Rosenfeld (161) modify the Cohn low-temperature ionic-strength principle and use it for measuring the fibrinogen levels of blood. Ratnoff & Menzie (162) determine fibrinogen by clotting plasma in the presence of crushed glass. The fibrin, adhering to the glass, can be removed by centrifugation and its tyrosine-like activity determined.

Platelets (thrombocytes).—It is generally agreed that platelets have both chemical and mechanical functions in blood clotting. For a long time the chief chemical function of platelets was thought to be the initiation of clotting by the release of thromboplastin. Now, however, a number of articles (94, 163, 164) stress the low thromboplastic content of platelets. Nevertheless, these reports need not vitiate the key role of platelets in supplying thromboplastin. Indeed, the slow clotting of shed blood (6 to 10 min.) collected under ordinary conditions attests to the fact that no great amount of thromboplastin is involved. In this regard, the report of Landwehr & Alexander (165) can be emphasized. These workers have determined the thromboplastic content of platelets, and report that per unit of nitrogen, the thromboplastic content is comparable to that of lung extract. It is obvious that statements regarding the degree of thromboplastic activity of various substances are meaningless, unless measured in terms of some yardstick such as that used by Landwehr & Alexander.

The importance of platelets in the clotting of blood is again confirmed

by Buckwalter *et al.* (166) in their study on prothrombin utilization of canine and human plasma. They find that, below a certain critical number of platelets, the prothrombin utilization decreases with decreasing numbers of platelets. Interestingly, they observe that numerically the requirement of dog plasma for platelets is about 1.7 times greater than for human plasma, and volumetrically the requirement is three times greater.

Besides thromboplastin, platelets are thought to contain other factors. One of these is described by Mann *et al.* (167, 168) as a prothrombin conversion factor. Ware *et al.* (164) confirm this observation and report the presence of another factor which they believe potentiates the action of thrombin on fibrinogen. Travis & Ferguson (169) fail to confirm this latter observation, but it is only fair to say that their experiments are not an exact duplication of the work of Ware *et al.* Zucker (170) finds that platelets contain a vasoconstrictor substance which she thinks is the same vasoconstrictor isolated from serum by Rapport (171).

Carr & Fowler (172) agree with Conley *et al.* (173) in failing to confirm the reports of Allen and co-workers that heparin or heparin-like substances are present in the blood of patients with thrombocytopenic purpura. They also find that thrombocytopenic blood shows increased sensitivity to the effect of heparin. This is not surprising in view of the fact that the coagulability of the blood is already disturbed by the reduction in the number of platelets.

It is generally agreed that platelets must undergo lysis before becoming effective in blood clotting. Certain surfaces, notably glass, are prone to produce platelet disintegration, whereas other surfaces, such as silicone or paraffin, delay platelet breakdown. The difference between surfaces is sometimes attributed to the wettability of the glass, and the nonwettability of the silicone surface. However, as Quick has shown (174), the problem is not this simple, since cellodion, a wettable surface, does not accentuate the lysis of platelets. Also, Moolten & Vroman (175) claim that platelets adhere as readily to a silicone surface as to a glass surface.

A number of other factors are thought to be responsible for platelet lysis. Brinkhous (176) presents evidence that plasma contains a platelet lysis which he believes is deficient in hemophilia. Zatti (177) and Fonio & Schwendener (178) show that thrombin causes profound alteration in platelets. Stefanini (179) makes the same observation. Quick *et al.* (180) amplify the observation of Zatti, giving great weight to the labilizing effect of thrombin on platelets. They assume that platelet lysis activates a circulating thromboplastinogen to thromboplastin, which in turn converts prothrombin to thrombin. The tempo of thrombin formation then becomes accelerated by the action of thrombin itself on platelets. As Brinkhous (181) has pointed out, this theory is based on two bits of evidence: (a) failure to demonstrate thromboplastin in platelets, and (b) variation in the rate of disappearance of prothrombin from plasma with different platelet levels. For a lively discussion of Quick's new theory, the fourth Macy report should be consulted (182).

The more mechanical aspects of platelet function include the work of Mann *et al.* (168) who studied the formation of fibrin in normal plasma collected in a silicone-coated container. They report that platelets serve as foci for the formation of fibrin network, but find no evidence for the direct initiation of fibrin formation. Moolten & Vroman (175) and Moolten *et al.* (183) investigate the adhesiveness of platelets using a glass wool filter. They indicate that this technique has diagnostic value in certain hemorrhagic diseases. Eisen *et al.* (184), using Moolten's method, report that dicumarol lowers platelet adhesiveness. They find a hyperadhesiveness in thromboangiitis obliterans and phlebitis. Wright (185) reviews her work on platelet adhesiveness in the 1951 Macy report.

Brecher & Cronkite (186) report on the inherent errors involved in platelet counts, and find that under certain conditions the error is no greater than that inherent in any hemocytometric method. They also study some of the variables that influence the morphology of platelets (type of surface used, concentration and type of anticoagulant, thickness of preparation, etc.). They stress the importance of considering these variables when correlating platelet alterations with changes occurring in clotting.

HEMOPHILIA

At present there are two viewpoints concerning hemophilia. One holds that the blood is deficient in a factor necessary for normal coagulation; the other, that an inhibitor is present which prevents normal coagulation. They both hold that the hemophilic platelet is normal. Brinkhous and Quick both subscribe to the deficiency theory. Brinkhous (176) presents evidence which he interprets as indicating the deficiency of a plasma platelet lysin [antihemophilic factor (AHF)]. Quick (94) believes that hemophilic plasma is deficient in a precursor of thromboplastin (thromboplastinogen) which is normally activated by platelets. Feissly (187) agrees with Quick. The work of Mond & Singer (188), however, appears to be inconsistent with Quick's interpretation. They did the rather obvious thing of adding aqueous homogenates of platelets to hemophilic blood. Such additions restore the clotting time to normal and alter the utilization of prothrombin. According to the Quick theory, the hemophilic plasma lacks the substrate on which platelets act; nevertheless, the clotting defect is corrected by the addition of platelets. The Brinkhous theory could explain this experiment on the basis that the homogenates contain platelets which had undergone lysis. Stefanini & Crosby (189), as well as Merskey (190), present supplementary evidence for the inherent adequacy of hemophilic platelets by showing a complementary correction when hemophilic blood is mixed with blood from a patient with thrombocytopenic purpura.

Graham *et al.* (191 to 195) report a method for the assay of AHF. They find that in normal blood, AHF rapidly disappears after clotting. Serum 1 to 3 hr. old has only traces of AHF. In plasma with low platelet counts, AHF disappears slowly. In citrated plasma freed of fibrinogen by heat coagulation, AHF remains, but on recalcification it disappears. This experiment shows

that AHF is not removed by fibrin but is involved in the first phase of clotting. They also report that canine plasma contains several times as much AHF as does human plasma. Shinowara (196) notes that ultraviolet radiation of plasma destroys the hemophilic corrective factor.

Brinkhous *et al.* (17, 197) use a strain of hemophilic dogs for genetic studies. As in the human, the disease is inherited as a sex-linked recessive characteristic. They have studied three of the five possible crosses in this type of inheritance. These include: heterozygous female with normal male, heterozygous female with hemophilic male, and a normal female with hemophilic male. From crosses of the heterozygous females and hemophilic males, female bleeders are obtained. They have raised the female bleeders to maturity and now plan to whelp them with hemophilic and normal males (197). In this connection, hemophilia can also occur in the human female, as indicated by the reports of Israël *et al.* (198) and Merskey (17).

Reference has been made to the use of the one and two stage prothrombin utilization assays on hemophilic serum. Neither test can be considered specific for hemophilia, but they do have value when correlated with other laboratory procedures. Brinkhous *et al.* (197) fail to find either of the tests of value in detecting canine female transmitters.

Reports dealing with the prothrombin consumption test include the papers by Alexander & de Vries (199), Soulier (200), and de Vries *et al.* (201). Orr & Gray (202) confirm Owren's original report that hemophilia is not due to a deficiency of factor V.

De Vries *et al.* (203) attempt to explain the paradoxical observation that although SPCA is low in hemophilia, the Quick one stage test on the same serum gives values several times higher than normal. Since the arguments advanced are somewhat tenuous, the reader should consult the original work.

Dreskin & Rosenthal (204) report a bleeder whose blood had a circulating anticoagulant capable of neutralizing the antihemophilic effect of normal plasma. Van Creveld *et al.* (205) add another case of hemophilia with a circulating anticoagulant to the 18 already reported in the literature. In their patient they find no evidence that the circulating anticoagulant is an antibody. Frommeyer *et al.* (206) describe a hemophilic who became refractory to the therapeutic benefits of blood transfusions. The reports of circulating anticoagulants lend credence to the aforementioned viewpoint of Tocantins as to the possibility of an inhibitor in hemophilia. Quick & Conway (207) describe "identical twins" only one of whom developed hemophilia.

INHIBITORS

Heparin and antithrombin.—It has long been known that, when whole blood clots, the thrombin formed is rapidly inactivated, partly by antithrombin and partly by adsorption on fibrin. In fact, Howell used fibrin as a starting material for the preparation of thrombin. However, from a physiological standpoint, the adsorption of thrombin by fibrin was not considered as important as its inactivation by antithrombin. It will be recalled that in

1942 Seegers *et al.* (208), working with purified thrombin, showed that heparin enormously increased the antithrombic activity of plasma, but in the absence of plasma, was not antithrombic. Evidence was presented that a cofactor in plasma determines the amount of thrombin destroyed, and heparin determines the speed of the destruction. Later, Astrup & Darling (209) emphasized the existence of two antithrombins: one was heparin which required a cofactor (coinhibitor), and the other was the so-called natural antithrombin. They believed that the two mechanisms could be dissociated and pointed out that bovine serum contains natural antithrombin and not heparin cofactor. On the other hand, plasma was said to contain both cofactor and natural antithrombin. Klein & Seegers (210) have recently reinvestigated the problem of the heparin cofactor. They find that defibrinated plasma produces 24 per cent inactivation of their purified thrombin, whether heparin is present or not. Whole plasma, without added heparin, causes 41 per cent inactivation, and when heparin is added there is 71 per cent inactivation. They therefore postulate that heparin increases the antithrombic activity by promoting the adsorption of thrombin on fibrinogen. They conclude that the cofactor of heparin (coinhibitor of Astrup & Darling) is fibrinogen itself. It is not clear, however, that fibrinogen accounts for all the cofactor activity since Astrup & Darling (209) find that heparin cofactor can be demonstrated in certain plasma fractions, even after fibrinogen is removed. Along this same line can be cited the work of Monkhouse *et al.* (211) and Warner's remarks (212) concerning the discrepancies between the identity of fibrinogen and heparin cofactor. Furthermore, it is difficult to reconcile the viewpoint of Klein & Seegers with the recent work of Snellman *et al.* (213). The latter, using entirely different methods, have fractionated the heparin-containing compound of mast cell cytoplasm. This complex contains three components—heparin, a polypeptide, and a lipid residue. The molecular weight of the polypeptide is about 8,000 and contains six amino acids. The lipid contains lecithin, cholesterol, and neutral fat. Their studies indicate that heparin in its native state is loosely linked to the lipoprotein (polypeptide plus lipid content). By themselves, neither the heparin nor the lipid nor the polypeptide have antithrombic activity. When all three components are recombined, however, antithrombic activity is restored. Electrophoretic studies indicate that the lipopolypeptide is similar to the heparin cofactor of serum. Also, electrophoretic studies show that the native heparin complex reacts with thrombin.

It would be of interest to see the work of Klein & Seegers repeated somewhat more quantitatively and particularly with the fibrinogen-free fractions of Astrup and the fractions of Snellman *et al.*

It can be added that the observations of Klein & Seegers are in agreement with the earlier conclusion of Quick & Favre-Gilly (95) that fibrin, by adsorbing thrombin, constitutes a potent "antithrombin." Johnston & Ferguson (91) also study the effect of adding heparin to defibrinated and non-defibrinated blood.

In the past two years very little has been contributed toward elucidating the *in vivo* anticoagulant activity of heparin. Howell originally believed that heparin blocked the conversion of prothrombin, presumably by uniting with the protein. Brinkhous *et al.* (214) showed that heparin requires a plasma cofactor to prevent the conversion of prothrombin to thrombin. Others have expressed the view that heparin is an antithromboplastin. Klein & Seegers (210) believe that heparin interferes with the thrombin-fibrinogen reaction, and that this reaction requires a plasma cofactor of the type originally described by Howell. Overman (124) advances the theory that heparin acts by combining with a cofactor in the form of a circulating thromboprotein, thereby releasing a powerful lipid anticoagulant. It is not at all certain how many of these cofactors are one and the same. Repeating some of these experiments with fractions obtained by Snellman *et al.* may help to clarify the problem.

Best & Jaques (215) have postulated that an enzyme, heparinase, destroys heparin, thus accounting for its short *in vivo* action (211). Conley *et al.* (216) and Applezweig *et al.* (217) incubate plasma with heparin but find no evidence for such an enzyme.

A number of reports give data concerning the action of either heparin or antithrombin, but the fundamental mechanisms are not analyzed. Shinowara (218) points out that *in vitro*, heparin may be either anticoagulant or coagulant, depending upon its concentration in the final clotting tube. Stefanini (219) finds that passage of carbon dioxide through plasma followed by ultrafiltration reduces the antithrombic titer. Udvardy (220) gives data on the antithrombic activity of serum from various species. Weber & Drechsler (221) study the *in vitro* effect of water-soluble vitamins on the antithrombic activity of serum. Kay *et al.* (222) report on the action of vitamin E and antithrombin, but their conclusions are not widely accepted (223). Hugentobler *et al.* (224) report that the serum antithrombic activity is increased in the presence of liver disease. Loomis (225) claims that heparin causes the elaboration of antithrombin from its precursor, proantithrombin. Nolf (226) states that tricalcium phosphate removes heparin from plasma but not antithrombin.

Halse (227) reports some interesting experiments concerning the effect of heparin on fibrinolysis. He produces localized thromboses containing radioactive material and finds that the subsequent administration of either heparin or thrombocid (a synthetic heparin-like compound) is associated with a greater release of the radioactive material into the general circulation, thus indicating that these anticoagulants cause dissolution of the clots. This work is certainly at variance with that of Jaques (228), and one suspects there is another explanation beside the lysis of the thrombus by heparin. Wright (229) uses a roentgenographic technique to study the effect of anticoagulants on dissolution of thrombi.

Swank (230) confirms the observation of Hahn (231) that lipemic plasma becomes less turbid after the intravenous administration of heparin. Prior

to this, Weld (232) suggested that heparin caused a clustering of the fat particles, but Swank now claims that at least part of the fat becomes adsorbed on erythrocytes. Swank further reports that, *in vitro*, heparin can cause clustering of the chylomicra, but one gets the impression that the process is slow and visible change in the plasma far less striking. Anderson & Fawcett (233) report that mixing lipemic plasma with plasma obtained after heparin injection causes gradual clearing of the former. Block *et al.* (234) study the effect of heparin in decreasing the turbidity of plasma in patients with arteriosclerosis. They find that, following alimentary lipemia, intravenous injection of heparin causes less translucency of the plasma than it does in normal controls.

Methods of determination of heparin in blood include those of Lewis & De Maria (235), Gibson *et al.* (236), and Meneghini & Cervini (237). Those interested in heparin assay should consult the article by Jaques (238). He finds that 100 ml. of normal blood contains 9×10^{-3} mg. of heparin.

Dicumarol.—Quick & Stefanini (90) agree with earlier workers that the basic defect in plasma from patients receiving dicumarol is a lack of component A (prothrombin), the same as in vitamin K deficiency. This conclusion is derived from a multiplicity of mixing tests done with eluates from normal dog plasma, eluates from normal chick plasma, eluates from plasma of vitamin K deficient chicks, eluates from plasma of dogs receiving dicumarol, and eluates from dog plasma treated with tricalcium phosphate. This data permits so many interpretations that the reviewers find it difficult to evaluate the conclusion given by the authors. In another paper, Quick & Hussey (239) make the point that free prothrombin is reduced, but the precursor of prothrombin remains unchanged for several days after therapy is begun.

In contrast to the Quick viewpoint that only prothrombin is affected by dicumarol, a number of workers now believe that dicumarol affects several other factors as well. Mann & Hurn (240), Olwin (241, 242), Owen & Bollman (243), Felix *et al.* (244), Brambel (245), Munro & Munro (246), Sternberger (247), Shinowara & Smith (248), and Koller *et al.* (44), all note that early in dicumarol administration there is a discrepancy between the various methods of prothrombin assays. Likewise, in this category is the report by Lein & Lein (249) who find that protein thromboplastic agents cause normal plasma to clot faster than lipid thromboplastins, but the reverse effect is obtained with dicumarol plasma. As Mann & Hurn (240) have pointed out, one can also include the reports from three other laboratories, that thromboplastin prepared from normal brains reacts differently with dicumarol plasma than thromboplastin prepared from brains of animals who have been given dicumarol. It is possible that the fundamental investigations with Tocantins' or Overman's inhibitor (to be discussed later) may unravel many of the seemingly unexplainable results. At this time, however, the only conclusion that can be safely made from these various reports is that they undoubtedly indicate the presence of another important variable or variables which must be controlled before further progress can be made.

Weiner *et al.* (250) report on the fate of ingested dicumarol in man. They observe that the peak plasma level of dicumarol (measured spectrophotometrically) occurs 24 hr. after its ingestion (10 mg. per kgm.), but the maximal effect on the prothrombin occurs in 48 hr. The dicumarol is slowly metabolized to unknown transformation products. The rate of elimination by the kidneys is quite negligible. Spinks, *et al.* (251) synthesize dicumarol containing C^{14} in the methylene bridge and administer it to rabbits and mice. The radioactive dicumarol disappears quickly from the blood and is recovered in the liver, bile, intestinal contents, and later in the urine. Ten per cent of the radioactive dicumarol is fixed in the liver. Administration of vitamin K causes an acceleration in the rate of removal of the dicumarol from the liver, thus explaining Link's observation (105) on the ability of vitamin K to reduce dicumarol-induced hypoprothrombinemia. Hausner *et al.* (252) gave radioactive dicumarol and Tromexan to animals. They believe their data indicates that the shorter hypoprothrombinemic action of the latter is due to its faster rate of metabolic turnover. Weiner *et al.* (253) confirm this.

James *et al.* (254), Shoshkes *et al.* (255) and Watkin *et al.* (256) report that an emulsion of vitamin K_1 oxide effectively counteracts the hypoprothrombinemia of dicumarol. In fact, this compound appears to be more effective than the other forms of vitamin K. Overman *et al.* (257) discuss some of the discrepancies of various reports anent the effect of vitamin K in dicumarol therapy. Lubran (258) and Roseman & Green (259) use colorimetric methods for measuring blood dicumarol levels.

Other inhibitors.—Tocantins believes that plasma contains a lipid inhibitor which he calls "antithromboplastin." Furthermore, the balance between antithromboplastin and thromboplastin is important in determining the speed of clotting. This work is reviewed by Tocantins & Carroll in one of the Macy reports (260). They purify antithromboplastin, using either plasma or Quick's thromboplastin as a starting material. It may seem anomalous that a procoagulant, such as thromboplastin, should be a rich source of anticoagulant, but this has been clearly demonstrated. Coon *et al.* (261) study the *in vitro* and *in vivo* effects of Tocantins' lipid inhibitor in dogs and rabbits, and report that both the plasma prothrombin and factor V levels are lowered. Independently, Overman & Wright (262) have prepared an inhibitor apparently identical to that of Tocantins. Furthermore, the methods of preparation suggest that the inhibitors of Tocantins & Carroll and Overman & Wright are similar to the one originally described by McLean (263), and still later by Chargaff (264). Tocantins *et al.* (132) believe that glass surfaces have a greater affinity for the inhibitor than silicone or paraffin surfaces. They stress the importance of avoiding glass if the effect of the inhibitor is to be demonstrated in normal blood or plasma. In this respect, too, Tocantins *et al.* (265) investigate what they call the "no-man's land" of the Quick test. Incidentally they call attention to the misleading custom of referring to the Quick test on 100 per cent plasma or 12.5 per cent plasma, when actually the stated percentage refers to the concentration of the starting material

and not the concentration of the plasma in the final clotting tube. In the Quick test on so-called 100 per cent plasma, the concentration in the final clotting tube is approximately 30 per cent (i.e., taking into account the addition of oxalate to the blood and the three-fold dilution when thromboplastin and calcium are added to the plasma). By the use of more concentrated reagents, Tocantins *et al.* are able to do the Quick test when the final clotting tube contains as much as 74 per cent plasma. Using silicone surfaces for these experiments, they report that, between concentrations of 37 and 74 per cent plasma, the clotting times increase with increasing concentrations of the plasma.

A report somewhat analogous to that of Tocantins *et al.* is one by Gollub *et al.* (266) who find that with brain thromboplastin, the thromboplastic activity varies inversely with the concentration of plasma.

Tocantins believes that his inhibitor is increased in hemophilia thus accounting for the delayed clotting. The evidence for this viewpoint is summarized in the last Macy report (267). He and Carrol (268) have assayed the inhibitor content of various tissues from hemophilic and normal patients. They report higher values of the inhibitor from the hemophilic tissues. At present, Tocantins' viewpoint on hemophilia is not widely accepted; nevertheless there are 19 reported cases of hemophiliacs with circulating anticoagulants.

Hecht (269) reports that the cephalin fraction of phospholipids contains glutamic acid and sphingosine, both of which delay the coagulation of chicken plasma. Fiala (270, 271) states that absorption of plasma with barium carbonate removes both prothrombin and an anticoagulant. The anticoagulant is separated from the prothrombin by dissolving the barium carbonate in acetic acid and dialyzing. Neither Hecht nor Fiala investigated the mechanisms of their inhibitor by using purified reagents.

Harrington *et al.* (272) report an interesting case with a prolonged Quick prothrombin time using human brain thromboplastin instead of rabbit brain thromboplastin. The addition of the patient's plasma to normal plasma caused the latter to give a prolonged one stage value. The factor responsible for the slowing was adsorbed by tricalcium phosphate. The authors believe they are dealing with a species specific inhibitor. Conley *et al.* (273) reinvestigated the case previously described by Chargaff & West (133), but unfortunately none of the blood clotting studies were done with human brain thromboplastin, making it impossible to say whether the patient resembles the one described by Harrington *et al.* (272).

Lüscher & Labhart (274) describe two cases of circulating anticoagulants in multiple myeloma. Both cases had a hyperglobulinemia. Uehlinger (275) reports another case of a circulating anticoagulant in a patient with hyperglobulinemia.

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BLOOD GAS TRANSPORT¹

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This review, like the 1950 review by Darling (1), is organized into three sections dealing with the stages in transport of normal respiratory gases: (a) the equilibrium at the lung barrier, (b) properties of blood as a carrier of gases, and (c) gas exchange in tissues. A summary of various factors and stresses affecting blood gas transport and developments in techniques and methods will follow. Pulmonary ventilation, circulation, external respiration and control have been omitted since these factors will be covered in other chapters.

ALVEOLAR-ARTERIAL EQUILIBRIUM

The standardization of definitions and symbols in respiratory physiology (2) facilitates the derivation and understanding of the mathematical expressions concerned in the interrelationships between "mean" alveolar air and the various components which determine its composition. The work of Riley & Cournand (3) and Rahn (4) in the formulation of these relationships has provided a basis both for understanding mutual interactions of the physiologic variables of pulmonary ventilation, perfusion, composition of gas, and blood phases and for testing the validity of the assumptions concerned. The study of these relationships is facilitated by the development and application of dynamic recording techniques. Fowler (5), Bateman, Boothby & Helmholtz (6 to 9), Luft and co-workers (10), Hitchcock & Stacy (11), Armitage & Arnott (12), and DuBois *et al.* (13) have contributed to progress along these lines. Combination of these continuous electronic gas analyzer and gas flow techniques with simultaneous dynamic measurements of blood composition, flow, and pressure is expected (14) to make possible more direct experimental approaches to these problems in the intact animal both in steady and in unsteady state conditions.

Application of the technique of Lilienthal & Riley to the study of alveolar arterial pO_2 gradients has continued (15, 16, 17) and the procedure has generally been verified (18) and extended (19). Morgan and co-workers (20, 21, 22) and Mangun and associates (23, 24) have attempted to apply direct polarographic and photometric recording techniques to this problem with some promise of success. It is generally conceded that, at least in conditions of normalcy and rest, the major portion of the alveolar-systemic arterial blood pO_2 difference arises from inequalities of ventilation-perfusion relationships (the exact nature of which is still to be elucidated) rather than a true

¹ The survey of the literature pertaining to this review was concluded in July, 1951.

alveolar membrane gradient. In addition to the clarification of the nature of alveolar samples made possible by continuous sampling and high speed electronic gas analyzers (25, 26, 27), Forssander & White (28 to 31) and Brown, Hatch & Cook (32) have developed improved methods for spot sampling of gas from the respiratory airway. The possibility of using isotopes in the study of dynamic alveolar and blood gas exchanges has not been fully explored (32 to 35).

PROPERTIES OF THE BLOOD CONCERNED IN GAS TRANSPORT

Studies bearing on the control and regulation of erythropoiesis cannot be completely covered in a review of this type. The reader is referred to review articles (36, 37, 38) for information concerning progress made in the elucidation of factors such as vitamin B₁₂ and folic acid related to the formation, maturation, and release of erythrocytes from the bone marrow. Horrigan and associates (39), from studies of the direct action of folic acid and vitamin B₁₂ on bone marrow utilizing staining techniques, conclude that these substances are concerned in the formation of nucleic acids in living cells.

The effect of anoxic anoxia on hematologic components in man has been well documented by Merino (40) and Chiodi (41). Attempts at elucidating the mechanism by which changes in arterial pO₂ regulate erythropoiesis have continued (42 to 49). Magnussen (50) reported that increase in carbon dioxide tension or decrease in pH inhibits red cell production in rabbit bone marrow. Studies by Drabkin & Graybiel (51) and Grant (52) indicate that production of new cells is a major component of the hematologic response. Reissman, utilizing the technique of parabiosis, has obtained additional evidence that a humoral mechanism may be involved (53). De Bias (54) found that testosterone stimulates erythropoiesis and suggested that the thyroid influences delivery of red cells from the bone marrow of rats. Erythropoietic response to hemorrhage apparently is not affected by adrenalectomy (55) or sympathectomy (56).

Consequent to the radiation hazards of this era, interesting factors affecting the susceptibility of hemopoiesis to exposure to roentgen rays have been described. Anoxia has been reported to increase the resistance to whole-body radiation in mice (57, 58). Jacobson and co-workers have found that protection of the spleen (59) and to a lesser extent other organs (60) provides marked protection because of rapid development of ectopic blood formation in protected areas (59 to 63).

Recent reviews should be consulted by the reader interested in the relationship of chemical structure to the respiratory function of hemoglobin and its physiologic properties (64) and in the breakdown of hemoglobin and porphyrin metabolism (65, 66, 67). Current concepts of iron metabolism are well reviewed by Rath (68) and by Finch *et al.* (69).

The kinetics of oxyhemoglobin dissociation have been studied by Roughton and associates (70 to 73) who have obtained evidence that there is a

physiologically significant difference between the velocity constants of the four intermediate reactions of oxygen with hemoglobin to form the fully oxygenated compound, Hb_4O_8 . Studies by Allen, Guthe & Wyman (74), however, indicate that the four oxygen combining centers of hemoglobin are identical. By utilizing simultaneous photometric and polarographic techniques and *in vivo* equilibration, Nahas *et al.* (75) have defined the dissociation curve at high oxygen tensions in man. Their results indicate that, under physiologic conditions, a tension of 400 mm. Hg is required to produce practically complete saturation of hemoglobin. These findings have been confirmed recently by Hickam & Frayser (76) using somewhat different methods.

The hemoglobin dissociation curve of children is reported by Morse, Cassels & Holder (77) to lie farther to the right than that of adults. Cyanotic congenital heart disease is associated with a further compensatory displacement to the right (78), thus favoring release of oxygen to the tissues. A shift to the right has also been reported in liver diseases (79). Penrod (80) found that the leftward shift due to decreased temperature in severe hypothermia in dogs did not cause hypoxia of the heart. Comparative physiologic studies on various hemoglobins have been reported (81, 82, 83).

Further studies of the time and oxygen tension required to produce hemoglobin saturation by inhalation of high oxygen mixtures using a Millikan oximeter have been reported by Douglas & Edholm (84) and by Knutson and co-workers (85) using an absolute reading type oximeter. Somewhat similar investigations have been carried out by Montgomery, Zinsser & Horwitz (86) utilizing a polarographic technique to record the oxygen tension in skin during oxygen inhalation. The possible errors in such oximetric measurements on heat-flushed ears have been emphasized by Elam and co-workers (87), who have reported phenomenally good results using improved procedures and an absolute reading type ear oximeter (88). Simultaneous measurements of rapid changes in blood oxygen saturation by ear oximeters on one heat-flushed ear, one histamine-flushed ear, and directly on arterial blood led Wood and associates (89, 90, 91) to conclude that the oxygen saturation, pressure, and circulation rate of blood in the ear flushed either by heat or histamine is, for practical purposes, arterial in nature. Stacy, Burch & Hitchcock have detected respiratory variations in the oxygen and carbon dioxide content of pulmonary vein blood in dogs (92).

Investigations on carbonic anhydrase pertinent to this review have been few. The role of metal ions (93) and zinc (94) in enzyme systems has been reviewed. Using improved methods, Clark & Perrin (95) could find no evidence that certain substances were activators of carbonic anhydrase. A method of determining carbonic anhydrase activity at body temperature is described by Altschule & Lewis (96). Ashby & Schuster (97) report evidence that the occurrence of carbonic anhydrase in the cerebrum of young dogs, rats, and rabbits is correlated with the onset of functional activity of this structure. The red cell content of carbonic anhydrase was found to be normal

in cyanotic heart disease (98) and sickle-cell anemia (99). The possibility of a relationship of carbonic anhydrase to production of hydrochloric acid by the stomach should be reconsidered in the light of the demonstration by Fürst *et al.* (100) that in hypocapnic rats, the blood carbon dioxide level was correlated with output of hydrochloric acid by the stomach.

GAS EXCHANGE IN TISSUES

Drabkin has attempted to elucidate the relation of cytochrome-*c* to the cellular utilization of oxygen by studying the tissue concentration of cytochrome-*c* in conditions affecting metabolism (101, 102, 103). His results (103) and those of Opitz & Samlert (104) indicate that there is a relationship between the metabolic intensity of tissues and their cytochrome-*c* content. Drabkin postulates that this relationship may be involved in the mechanism of control of metabolic rate by thyroid hormone. Possible beneficial effects of administered cytochrome-*c* in anoxia of human beings (105) have not been confirmed by more critical experiments in animals (106). Beinert and co-workers have studied the metabolism of injected cytochrome-*c*, using isotope techniques, and find no evidence that administered cytochrome is incorporated or utilized by the tissue cells of recipient animals (107, 108, 109).

Horwitz and associates (110) have studied the effect of changes in temperature on the oxygen tension in the skin of the extremities and have demonstrated effects probably related to the relative magnitude of temperature effects on the circulation rate to, and metabolic rate of, the tissues involved. Olsen & Schroeder (111) demonstrated a decrease in oxygen tension and pH in ischemic kidneys. The significance of the flicker fusion threshold as an indicator of changes in the degree of sufficiency of oxygenation to retinal-cortical structures is not clear (112, 113, 114). Various factors affecting metabolic activity of tissues have been investigated. Bigelow *et al.* (115) found no evidence of tissue oxygen deficit in hypothermic dogs. The oxygen utilization of cardiac muscle was found to be a linear function of the logarithm of the temperature by Fuhrman and associates (116). The effects of the adrenal glands (117), folic acid (118), thyroxine (119, 120), and barbiturates (121, 122) on metabolic activity have also been investigated. The apparent marked increase in metabolic rate after resumption of the supine position following passive standing has been demonstrated by Rahn & Ament (123) to result from the return of pooled venous blood from the extremities and the paying off of tissue oxygen debt developed during passive standing. The cause of respiratory symptoms induced by sudden withdrawal of ACTH has not been elucidated (124).

Cerebral.—The interested reader should consult the recent review by Schmidt (125). The nitrous oxide technique for cerebral blood flow has been applied in a variety of experimental and clinical conditions. In general, results show that level of oxygen utilization by the brain is maintained relatively constant in the normal person, even under conditions of moderate

stress (126). Scheinberg & Stead (126), Shenkin *et al.* (127), Wilkins, Bradley & Friedland (128), and Henry and co-workers (129) have investigated the effect of gravitational stress on cerebral circulation. Scheinberg has investigated possible errors in sampling from only one jugular vein (130) and evidence of contamination by extracerebral blood (131). He finds cerebral metabolism to be normal in hyperthyroidism (132) but to be reduced in myxedema (133) and pernicious anemia (134) in proportion to the severity of neurologic involvement. Kety and co-workers (135, 136), Bentinck and associates (137), and Shenkin and associates (138, 139) have investigated the effect of various drugs, stellectomy, and spinal block on cerebral circulation.

Myocardial, splanchnic, and renal.—The results of Gregg *et al.* (140) in comparing the nitrous oxide method with direct measurement of coronary flow indicate that the nitrous oxide method is semiquantitative in nature. Comparable coronary flow values in unanesthetized dogs and in man by Bing and associates (141, 142) are in close agreement.

The sulfobromophthalein method and cardiac catheterization have been used by Myers, Brannon & Holland to demonstrate an increased splanchnic oxygen consumption in hyperthyroidism (143) and by Wilkins and co-workers (144, 145) to investigate vasoconstriction in the splanchnic organs during the upright position mediated by the sympathetic system (144, 145).

Conn & Markley (146) and Study & Shipley (147) have obtained close agreement between direct measurements of renal blood flow and calculated Fick values using diodrast or *p*-aminohippurate. During renal nerve stimulation, however, the Fick values were found to be too low (147). The effect of anoxia on renal blood flow has been studied by Franklin, McGee & Ullmann (148, 149), by Berger, Galdston & Horwitz (150) and by Kreienberg, Prokop & Schiffer (151). Evidence of the diversion of cortical blood flow found in rabbits was abolished by denervation of the kidney (149). Indirect measurements of effective blood flow to tissues by recording the rate of disappearance of injected electrolyte or nonelectrolytic solutions have been reported (152 to 155).

CARBON MONOXIDE

Clark and co-workers have demonstrated the oxidation of carbon monoxide to carbon dioxide in the intact animal (156) which apparently occurs mostly in muscle tissue (157) at a rate which in man would be approximately 20 ml. per hr. when respiring a mixture containing 0.07 per cent carbon monoxide (158). Sjöstrand (159, 160, 161), on the basis of alveolar air measurements, concludes that significant endogenous carbon monoxide formation occurs in man which is accelerated in hemolytic conditions. Carbon monoxide formation was also demonstrated in stored blood with evidence that the reaction depends on the conjoined presence of cells and plasma (162). The relationship of the concentration of carbon monoxide in air to the level of carboxyhemoglobin produced in the blood is discussed by Sroka (163).

Pace, Strajman & Walker (164) have found that breathing of oxygen at $2\frac{1}{2}$ atm. pressure will reduce carboxyhemoglobin concentrations to safe limits within a period of 1 hr. Such a procedure would be tolerable in regard to production of oxygen poisoning, and the possibility of supplying a large portion of body oxygen requirements from physically dissolved oxygen would be desirable in severe degrees of poisoning. Since only a slight increase (16 per cent) in cardiac output occurs during adaptation to severe chronic carbon monoxide poisoning in spite of the fact that venous pO_2 values remain low (25 to 30 mm. Hg), Asmussen & Vinther-Paulsen (165) conclude that tissue pO_2 cannot be regarded as a major factor in the regulation of cardiac output.

ALTITUDE

The multitude of reports precludes, because of space limitation, a critical discussion of investigations during the last three years on the effects and adaptive mechanisms to anoxia pertinent to blood gas transport. The work related to aviation medicine carried out in Germany during and immediately after World War II has been reviewed in detail (166). Investigations on decompression sickness carried out in the United States during this same period have also been reviewed (167). It has been demonstrated that a large part of acclimatization to altitude is concerned with adaptation to the lowered pCO_2 resulting from hyperventilation. Consequently there have been many investigations concerning acid-base changes during anoxia, effects of hyperventilation and related variables (168 to 179). Acclimatization can be divided into an initial stage characterized by hyperventilation and alkalosis and a secondary stage characterized by restoration of blood pH to normal in the presence of a low alveolar pCO_2 , making possible a maintained compensatory increase in alveolar pO_2 produced by increased alveolar ventilation [Rahn & Otis (168); Riley & Houston (177)]. Other variations in glucose (180), ketosteroid (181), and ascorbic acid (182, 183) metabolism perhaps related to hyperventilation have been studied. It has been demonstrated that over-all reduction in metabolism associated with reduction in body temperature plays an important role in the adaptation of rodents and lower animals to low barometric pressure (184 to 193). The effects of acclimatization in rats have been investigated by Altland (194) and by Wilhelm and associates (195). The effects of anoxia on the gut have been studied (196 to 200). The incidence of decompression sickness in World War II has been reviewed by Rafferty (201). Much study has been devoted to the effects of anoxia on the circulation and circulatory adjustments to anoxia (202 to 211). Hematologic adaptations to anoxia produced by emphysema (212), congenital heart disease (213), and histotoxic anoxia (214) have been described. Exposure to high altitude did not stimulate myohemoglobin production in dogs [Bowen & Eads (215)]. Hull (216) has studied the respiratory responses of dogs to anemic anoxia.

The problems of blood gas transport in the fetus and anoxia in the new-

born have been reviewed by Windle (217), Smith (218, 219), and Reardon and co-workers (220). Crehan and associates (221) found that the arterial saturation of newborn infants increased rapidly after birth from an average value of 57 per cent at 3 min. of age to 82 per cent at 10 min. and 92 per cent 2 hr. after birth. Miller and co-workers (222, 223) report that the resistance to anoxia of newborn guinea pigs is inversely related to the body temperature.

The effect of exposure to moderately high altitudes on the higher brain centers has received considerable attention (224 to 227), and the efficacy of various drugs in combating the effects of mild anoxia in man (228, 229) and severe anoxia in animals (230, 231, 232) has been investigated. A number of studies have been conducted on specific sites of action of anoxia on the central nervous system (233 to 240). Noell & Chinn's investigations of the site of failure in the visual pathway during anoxia are of special interest in aviation physiology (237, 238).

The practically important question of the duration of useful consciousness after acute exposure to severe anoxia has been further investigated and equations have been derived by Webster & Reynolds (241) relating the ambient pressure to the duration of consciousness after exposure to this pressure. The "reserve time" of warm blooded animals after explosive decompression or occlusion of the neck has been studied by Opitz & Thorn (242) and has been found to be increased in acclimatized animals. This increase with acclimatization may be related to the increased vascularity of the retina demonstrated in acclimatized animals (243) and in man (244). The time of useful consciousness after exposure to moderate altitudes, investigated by Wilson & Comfort (245) and Hall & Hall (246), is considerably shortened when air is breathed because of the nitrogen dilution effect. In rapid decompression to altitudes of more than 52,000 ft., Luft *et al.* (247) found that the latent period to loss of consciousness was 15 to 17 sec. and that it was little affected by air or oxygen breathing. This latent period is made up of the circulation time from lung to brain, the desaturation time of the blood, and then the 5 to 7 sec. which represent the reserve time of the brain proper to sudden anoxia such as occurs during sudden exposure to positive acceleration (248). If exposure to a pressure altitude of 52,000 ft. exceeds 5 or 6 sec., loss of consciousness occurs after the usual lapse of 15 to 17 sec. in spite of immediate recompression being completed 7 to 10 sec. earlier.

The physiological, physical, and biophysical aspects of explosive decompression have assumed increasing practical importance paralleling developments in extremely high altitude pressurized cabin aircraft. Equations describing the physical process of explosive decompression were derived by Haber (249). Luft *et al.* (250) have investigated the composition of alveolar gases in man during rapid decompression to various altitudes including 52,500 ft. The physiologically interesting phenomenon of oxygen passing from the blood into the alveoli occurs whenever the pO_2 of mixed venous

blood exceeds the alveolar pO_2 ; this situation pertains immediately after explosive decompression to 32,800 ft. when breathing air and at 48,000 ft. when breathing oxygen. The rate of oxygen loss during the first 5 sec. at 50,000 ft. is 212 cc. per min. with an accompanying threefold increase in excretion of carbon dioxide. Findings of other investigators (251 to 257) confirm the occurrence of minimal injury due to the physical aspects of the explosive decompression and emphasize the importance of the anoxic anoxia produced.

HIGH OXYGEN PRESSURES

Effects of inhalation of oxygen have been reviewed by Berger & Davenport (258). The mechanism of the convulsions produced has as yet not been settled. The potentiating effect of carbon dioxide on the convulsive action of oxygen has been confirmed (259 to 262). The investigations of Lambertsen and associates (263 to 266) failed to confirm the finding of markedly increased blood or tissue carbon dioxide tensions prior to oxygen convulsions and do not support the hypothesis that increased carbon dioxide tension is an important factor in development of oxygen convulsions. Breathing of 2 per cent carbon dioxide in oxygen at $2\frac{1}{2}$ atm. pressure increases cerebral blood flow in man so that internal jugular pO_2 is increased, thus possibly hastening the onset of oxygen convulsions due to exposure of a larger bulk of the brain to higher, presumably more toxic, levels of oxygen tension. Hemingway (267) found high oxygen tensions to be a more potent stimulus for pulmonary edema formation in guinea pigs than anoxia.

The physiologic mechanisms of the stimulating, anesthetic, and convulsive effects produced by breathing increased concentrations of carbon dioxide have been investigated by several groups of workers (268 to 277). Schäfer (275) found that long exposures to 3 per cent carbon dioxide produced a period of stimulation followed by depression in man and animals. The excitability of the respiratory center was decreased and the alkali reserve of the blood was increased because of retention of base by the kidneys.

Investigations of the uptake and elimination of inert gases by the body have continued (278, 279, 280). Tobias *et al.* (278) were able to express the uptake and desaturation curves of radiokrypton in terms of the sum of three superimposed components changing as a simple exponential function of time. Margaria & Sendroy (279) could adequately describe nitrogen elimination by two exponential decay curves. The elimination of the first component was related to circulatory rate and could be accelerated 20 per cent in the first half hour by breathing 5 per cent carbon dioxide in oxygen. The pressure of argon required to produce narcosis (41 atm.) in frogs was found to be much less than that for nitrogen [Marshall & Fenn (281)]. Helium was not narcotic and has been found to increase metabolism (282). Bean (283), on tenuous evidence, concludes that the narcotic effect of nitrogen is due to interference with the excretion of carbon dioxide. Cullen & Gross

(284) produced surgical anesthesia in man with a mixture of 80 per cent xenon and 20 per cent oxygen, while krypton was only slightly anesthetic.

ASPHYXIA

Draper and associates (285, 286, 287) and Shires & Eyer (288) have continued investigation of the interesting physiologic effects produced by diffusion respiration. Complete lack of electrical activity of the brain averaging more than 25 min. in duration has occurred in dogs with subsequent complete, permanent recovery. Sarnoff *et al.* (289), using differential bronchspirometry, demonstrated that stimulation of only one phrenic nerve causes ventilation of both lungs, probably because of transmission of fluctuating pressure associated with shifting of the mediastinum.

The effectiveness of resuscitators and other means of artificial respiration has been studied (290, 291, 292). The relative inefficacy of the Schafer method has been confirmed by Asmussen & Nielsen (291). The recovery of dogs from fresh water drowning depends on the amount of water that has entered the lungs and blood stream and not on the use of various types of resuscitation [Fainer, Martin & Ivy (293)]. Swann & Brucer (294, 295, 296) have reported extensive studies of the circulatory and biochemical events produced by acute anoxia from various causes in dogs and the requirements for effective resuscitation. Binet & Strumza (297, 298) have studied the arterial oxygen saturation associated with anoxic apnea in dogs and report that artificial respiration delayed recovery of spontaneous respiratory activity and did not increase percentage of survival. Arterial saturation levels associated with voluntary apnea are reported by Lemaire (299).

OXYGEN THERAPY

Several recent reviews concerning this subject are available (300 to 303). The problem of cyanosis has been reviewed by Selzer (304), and its relationship to arterial saturation has been subjected to further study by Geraci & Wood (305). Deleterious effects following oxygen inhalation are more likely to occur in anoxemia [Comroe, Bahnson & Coates (306)], perhaps related to the depression of respiration and further resulting accumulation of carbon dioxide [Motley (307)]. The danger of severe respiratory acidosis occurring in acute poliomyelitis in the presence of a normal arterial oxygen saturation is emphasized by the studies of Plum & Wolff (308). The paradoxical effect of oxygen inhalation following acute anoxia may be related to hypocapnia (309). Brown & Miller (310) produced cardiac arrhythmias in all and cardiac arrest in seven of ten dogs by sudden hyperventilation with air following a 2-hr. period of breathing 40 per cent oxygen.

CARDIAC OUTPUT BY BLOOD GAS MEASUREMENTS

Comparison of simultaneous determinations of cardiac output by the direct Fick method and direct volumetric measurements by rotameter

have been reported by Huggins, Smith & Sinclair (311) and Seeley, Nerlich & Gregg (312). There was no systematic deviation between the two methods; however, an indication of the accuracy of the Fick procedure is perhaps reflected in the average deviation of 7 (range, -29 to +26) per cent which was obtained. A similar degree of variability in direct Fick values was obtained by Griffin, Wood & Essex (313).

Cardiac output measurement based on carbon dioxide equilibration in alveolar air has been further investigated by Forssander and associates (314, 315, 316). Promising results were obtained using improved methods of sampling and accurately adjusted gas mixtures permitting equilibration during the course of one breath. Use of continuous high speed carbon dioxide gas analyzers would considerably facilitate the procedure [Hemingway (317)]. Chapman and co-workers (318) found that the acetylene method overestimates the arteriovenous oxygen difference by about 24 per cent, probably because of the increase in arterial oxygen content produced by the overbreathing utilized in the acetylene technique.

GAS TRANSPORT DURING ANESTHESIA

Multiplicity of investigations related to blood gas transport in anesthesia precludes individual mention (319 to 331). The factors governing uptake of anesthetic gases by the body have been reviewed by Kety (319). The demonstration by Beecher & Murphy (325) of severe acidosis occurring in thoracic operations related to inadequate ventilation [Roos & Gabbard (331)] is of considerable practical importance. The over-all oxygen consumption is demonstrated to be reduced during surgical anesthesia [Shackman, Graber & Redwood (332)]. Wechsler, Dripps & Kety (333) demonstrated a depression of cerebral oxygen consumption in spite of adequate blood flow.

A number of investigations pertinent to the physiology of blood gas transport have been carried out on clinical material (334 to 337). Improved measuring techniques have been used to study intrapulmonary mixing of gases and elimination of inert gases by Bates & Christie (334), Miller *et al.* (335), Robertson, Siri & Jones (336), Briscoe, Becklake & Rose (337) and Fowler & Blakemore (338). The pulmonary function and respiratory responses in emphysema and various types of pneumoconiosis have been investigated by Donald & Christie (339, 342) and by Wilson (340), West (341), and Motley and their associates (343). Gaensler & Carter report (344) a marked improvement in pulmonary function of emphysematous patients following repeated production of pneumoperitoneum. The mechanism of this effect is not clear. The studies of Burnett *et al.* (345) and Cournaud *et al.* (346) on the physiologic effects of pneumonectomy emphasize the remarkable capacity of the remaining lung to maintain nearly normal function in the usual case. Black & Roos (347) have demonstrated that diagnostic instillation of lipiodol into the pulmonary tree has very little effect on alveolar gas exchange unless very severe impairment pre-exists.

Demonstration of the feasibility of cardiac surgery and the limitation of techniques imposed by the necessity of maintenance of cardiopulmonary function has stimulated attempts to develop practically applicable extracorporeal pump-oxygenator circuits. The reports show promise of success (348 to 354). Intravascular administration of oxygen in practically important amounts is still not promising (353, 354, 355). Maintenance of dogs whose only source of oxygen was administered by gas dispersion into blood circulating outside the body has, however, been accomplished by Clark and associates (356, 357). The possibility of using a volunteer to oxygenate and circulate the blood of a patient undergoing intracardiac surgery has been demonstrated to be feasible by the artery-to-artery cross circulation studies in a man carried out by Bierman and co-workers (358).

METHODOLOGY

A description of current methods utilized in pulmonary function tests prepared by Comroe (359) will serve as a convenient reference for workers in this field, as will the second volume of Glasser's *Medical Physics* (360). Frequently experienced difficulties with manometric determination of blood oxygen, caused by hemolyzing agents of insufficient activity, are reflected by the appearance of four reports on this subject (361 to 364). Modification and application of Scholander's micromethod for determination of plasma carbon dioxide have been described by Holmes (365) and by Fürst & Mørstad (366, 367). Goldstein and associates (368) have described a modification of the Van Slyke-Neil technique for use in the presence of ethyl ether. Gas analysis methods with anesthetic gases are described by Ringrose, Rowling & Harbord (369) and by Prime (370).

Various modifications of methods for determination of blood hemoglobin, hematocrit, and red cell count have appeared (371 to 380). A method for determination of small amounts of carbon monoxide in blood is described by Siösteen & Sjöstrand (381). Improved procedures for determination of pH of whole blood with a glass electrode are reported by Wilson & Ognanovich (382).

Further modifications and applications of the oxygen cathode technique are reported (86, 110, 383 to 391), and likewise there have been a number of developments and applications of electronic gas analyzers (388 to 393) in addition to those mentioned previously.

The interest in photoelectric determinations on whole blood has continued. The present status of oximetry has been reviewed by Comroe & Wood (394), Wood (395), and Burchell (396). Kramer and co-workers (397) have made a notable contribution to future oximeter design by clarifying the various factors which affect the optical transmittance of blood. Paul (398) has described the use of modulated light, and Guyton, Gillespie & Armstrong have described (399) an ingenious method for obtaining an infrared cell whose output is independent of blood oxygen saturation. Brink-

man and co-workers (400, 401, 402) and Gross (403) have described oximeters using reflected rather than transmitted light. Application of this type of oximeter to anesthesia is reported by Boere (404).

Standard spectrophotometers have been used by Hickam & Frayser (405) and by Nahas (406) for determination of oxyhemoglobin and total hemoglobin content of hemolyzed blood as well as for carboxyhemoglobin by Klendshoj, Feldstein & Sprague (407).

Both cuvette and earpiece oximeters have recently been applied to cardiac output and blood volume determination by the dye dilution method (408 to 414) and by an indirect Fick procedure (88, 415) described by Matthes. The Millikan oximeter earpiece has been utilized by Watkins (416) for determination of the oxygen saturation of whole blood *in vitro*. Other versions of ear oximeters have been developed as an hypoxia warning device by Kramer, Timmons & Mayne (417) and for determination of arterial pressure [Uzmann & Wood (418)]. Callebaut, Denolin & Leguime describe utilization of the oximeter in studies of congenital heart disease (419) and for measurement of circulation velocity (420, 421). Other studies involving oximetry have been mentioned previously (85 to 91).

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PERIPHERAL CIRCULATION¹

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BIOPHYSICAL ASPECTS

Blood viscosity.—The original observations of Fahraeus & Lindquist (1) that the effective viscosity of blood is greatly reduced in small glass capillaries have been extended by Müller (2), who has obtained pressure-flow data for blood flowing in tubes ranging from 2 cm. to 8 μ in diameter. For a given hematocrit and flow velocity, the apparent viscosity decreases with decreasing tube diameter, even to the point where the tube diameter is comparable with that of the red blood cell; in the smallest tubes at suitable rates of flow, the blood viscosity may be little more than that of plasma. Similar results with artificial suspensions had previously been obtained by Müller (3, 4) and by Heinrich (5). Bayliss (6) has reviewed the basic physical problems involved and has presented new data on blood flow through capillaries of corpuscular dimensions, on the temperature coefficient of apparent viscosity and on the relations between viscosity and hematocrit. Empirical equations are presented to predict the apparent viscosity as a function of tube diameter, hematocrit, and rate of flow, but the basic physical laws involved remain unknown. The influence of corpuscular shape has been investigated by Suter (7), who found that, for a given hematocrit, tube diameter, and flow rate, the apparent viscosity of frog's blood containing large ellipsoidal erythrocytes is greater than that of ox blood containing small discoidal red cells. The change of shape of human red cells caused by sickling at low oxygen tensions has been shown by Ham & Castle (8) to produce a large increase of viscosity as measured in low velocity viscometers [cf. (9, 10)]. Extensive measurements by Kreuger (11) demonstrate that even plasma shows anomalous viscous properties at low rates of flow in very small capillary tubes. However, at high rates of flow in fully dilated blood vessels, anomalous flow effects are small. Mendlowitz (12) has studied pressure-flow relationships in dilated arteriovenous anastomoses of human digits and finds that in these vessels, as in fully dilated vessels of perfused extremities (13, 14), the flow is for all practical purposes proportional to the pressure. It is of interest that none of these investigators reports a measurable yield pressure, and it would therefore appear that blood flow through tubes is of the Newtonian type rather than the plastic type suggested by Lamport (15). The possibility remains, however, that plastic flow may occur in tubes which are so small that the corpuscles must be deformed in the flow process.

Preliminary theoretical and experimental studies on the physics of pulsating flow have been reported by Müller & Lambossy (16, 17), but so far these studies have been confined to ideal fluids. The recent development of

¹ The survey of the literature pertaining to this review was concluded in July, 1951.

electrical methods to record rapid changes of pressure (18 to 21), flow (20, 22, 23), and orientation of the red cells in the flow stream (24) may allow further advances in this fundamental but extremely difficult field.

Flow through stenotic apertures.—Gorlin & Gorlin (25) applied hydraulic equations for orifice flow to the calculation of the effective area of stenotic mitral valves in human subjects. The equivalent orifice area, as calculated from mean flow (cardiac output/diastolic filling time) and mean pressure difference, was surprisingly close to the anatomical area of the stenosed valve determined at necropsy. In a series of patients Gorlin *et al.* (26) found that the clinical evaluation of the severity of stenotic lesions correlated reasonably well with calculated equivalent orifice areas. Gupta & Wiggers (27) and Gupta (28) studied dynamic pressure relationships during experimental coarctation of the aorta in anesthetized dogs. Under these conditions a reduction of about 50 per cent on the lumen of the aorta was required to produce substantial alterations of pressure. They point out that altered pressure relationships in severe coarctation are partly a result of the decreased volume of the distensible aorta available for damping out the stroke volume. Flasher *et al.* (29) have studied the arterial dilatation which occurs distal to arterial stenoses in chronic experiments; they showed that post-stenotic dilatation occurs in renal arteries provided that the stenosis is sufficiently severe to produce hypertension and the development of collateral circulation. The mechanism of this interesting phenomenon remains obscure.

Physical properties of blood vessels.—Burton (30) has discussed physical equilibria in blood vessels from the point of view of Laplace's theorem which states that in a thin-walled cylinder of radius r , $T = Pr$ where T is the tension in the wall per unit length and P the pressure within the lumen. In applying this formula to blood vessels in which the wall thickness is appreciable, it is necessary to use an integrated value for mean tension. Burton points out that the wall tension required to resist physiological pressures decreases enormously in going from large to small blood vessels. Thus, the tension in arteriolar walls is less than 1 per cent of that in large arteries, and only a slight increase of tension is required for arteriolar constriction against the internal hydrostatic pressure. If the total tension in the wall consists of elastic tension plus a *constant* active muscular tension, then as the internal hydrostatic pressure is lowered, there will come a point of instability at which the vessel must collapse—the "critical closing pressure." In succeeding papers by Burton and his associates, experimental evidence is advanced to test this theory in the peripheral circulation. Nichol *et al.* (31) found that a critical closing could be demonstrated from pressure-flow curves in the perfused hindlimbs of frogs and rabbits and in the perfused rabbit's ear. The critical closing pressure was found to be elevated as predicted when the active tension was increased by vasoconstrictor substances. Studies on the effects of epinephrine (32) and sympathetic stimulation (33) were reported by Girling. A critical evaluation of this important work might include consideration of the absolute values of flow which appear to be too low to sup-

port the metabolism of the tissue and which are comparable in magnitude with fluid shifts across the capillaries in hindlimb preparations (34). Control experiments utilizing a rise of venous pressure rather than a fall of arterial pressure would be of interest, for in this case the theory would predict no vascular collapse and the flow should depend only on the arteriovenous pressure difference.

Physical methods, pressure, and flow.—An outstanding advance in recording of rapid changes of pressure within the heart and large vessels is described by Gauer & Gienapp (35). The pressure pickup consists of a miniature transformer with pressure-sensitive core; the unit can be attached to the end of a catheter and placed at the site of measurement. The characteristics of the instrument and typical records of intracardiac pressures free from catheter whip artifacts are illustrated by Ellis *et al.* (36). Hansen & Warburg (37) describe a modification of their capacitance manometer which allows recording of differential pressures. Techniques for determining the dynamic response characteristics of manometer systems by means of sine wave or step function pressure generators have been described by Isaacson & Jones (38) and by Parnell *et al.* (39). Landowne (40) has described a new technique for the study of pulse wave velocities: mechanical impacts are delivered to the artery from the skin at a frequency of 10 per sec. throughout the cardiac cycle, and the pressure distortions so produced are recorded distal to the point of impact. Jochim (41) has utilized electrical analogs for the analysis of pressure and flow transients in the carotid arteries.

A flowmeter of low hydrodynamic resistance which may be suitable for recording of blood flows in the liters per minute range has been described (42). It consists of a dynamically balanced rotor and magnet; rotation of the unit in the flow stream is proportional to flow and is said to be insensitive to alterations in viscosity or density. Revolutions per minute, and hence flow rate, may be recorded electrically from an external sensing coil and integrating circuit. Modifications and improvements in the design of electromagnetic flowmeters have been described by Clark & Randall (23) and by Arnold (43). Phasic changes of pulmonary flow have been recorded by Baxter & Pearce (44) utilizing a pitot tube, differential capacitance manometer, and an automatic device to compensate for the square-law relations between differential pressure and flow.

Details of the impedance plethysmograph for the study of blood flow and volume pulses are given by Nyboer (45, 46). Physiological and clinical applications have been explored by Nyboer *et al.* (47) and by McLean (48). Juster & Ingraham (49) report improved electrodes and recording system for measurement of blood flow by the conductivity method.

FLOW THROUGH CERTAIN ORGANS

Brain.—A comprehensive review, covering 431 references to the circulation and metabolism of the brain, has been published by Opitz & Schneider (50). The review is written from the point of view of Krogh's diffusion theo-

ries (51) relating blood flow and vascularization to oxygen consumption. Data are presented showing the effects of oxygen and carbon dioxide pressures on cerebral flow and oxygen consumption of anesthetized dogs. It is shown that a critical venous oxygen pressure exists (about 20 mm. Hg) below which the brain becomes diffusion limited. In this country, the nitrous oxide method of Kety & Schmidt (52) has been applied to various clinical conditions. Scheinberg (53) has shown that the brain does not share the generalized increase in circulation and metabolism caused by hyperthyroidism, whereas both are considerably reduced in myxedema (54). Shenkin (55) has investigated the action of various drugs on cerebral blood flow in man and also reports that bilateral stellectomy is effective in increasing flow (56). Mangold *et al.* (57) find a slight increase in cerebral flow during natural sleep, but no significant change of metabolism. By direct observation, Huerkamp & Rittinghaus (58) have compared the reactions of the retinal vessels with those of the pia; in general, the reactions are similar except that retinal vessels appear to dilate rather than constrict during apapnia or injections of calcium ion.

Kidney.—The flow properties of the kidney are unique in that blood flow is relatively independent of pressure in the physiological range of pressures (59, 60, 61). The mechanism of this "intrarenal" control of flow is unknown and continues to present a major problem in renal hemodynamics. The problem has been given added interest by the experiments of Spencer (62), who has shown that in dogs the flow appears to be independent not only of pressure but also of "viscosity" as this is increased in acute or chronic experimental polycythemia. Although the plasma flow (C_{PAH} , *p*-aminohippurate clearance) was diminished, the whole blood flow calculated from C_{PAH} and hematocrit was unchanged even when the hematocrit was increased to 70 per cent. Since the creatinine clearance was also unchanged, the filtration fraction increased greatly, often to 0.5 or 0.6. This gives rise to an enigma, for if the plasma were concentrated by more than two-fold the protein concentration would rise from 6 to 7 gm. per cent to 14 to 16 gm. per cent corresponding to a protein osmotic pressure of approximately 100 mm. Hg (63). Since mean arterial pressure was hardly more than this, it is difficult to understand how filtration could proceed unchanged as it evidently did.

Several short notes have appeared relating to intrarenal shunts. Block *et al.* (64), Houck (65), Scher (66), and Moyer & Handley (67) were unable to demonstrate shunts during stimulation of the renal nerves in dogs, cats, or rabbits. Lampert (68) makes the point that complete shutdown of either limb of parallel glomerular intrarenal circuits would not affect flow through the other limb by more than 10 per cent. Grossman *et al.* (69) did not find evidence of intrarenal redistribution of flow in patients with congestive heart failure; in such patients C_{PAH} and C_{IN} (inulin clearance) are greatly reduced (70).

The effects of exercise were investigated by Carlin *et al.* (71), who found

that in the dog, in contrast to man (72), moderately severe exercise was not accompanied by a decrease in C_{IN} or C_{PAH} . Pfeiffer & Wolff (73) found that considerable decrease of C_{PAH} occurs in humans during emotional stress induced psychiatrically and that the changes are more severe in hypertensives. Similar results were found by Koza *et al.* (74) during infusion of epinephrine. Reubi (75) has described a new phthalazine derivative which increases renal blood flow considerably; previously, the only agents known to increase flow in kidneys of normal humans were certain pyrogens.

Viscera.—Markowitz & Rappaport (76) have reviewed the circulatory physiology of the liver with particular emphasis on the hepatic artery. Their original observations showing that fatalities owing to ligation of the hepatic artery may be avoided by large doses of penicillin postoperatively have been confirmed in detail by Tanturi *et al.* (77). The suggestion is made that the hepatic artery normally provides a sufficiently high pO_2 to inhibit lethal anaerobic activity of organisms present in the liver. The effects of posture on liver blood flow have been studied by Culbertson *et al.* (78), using the brom-sulfalein (BSP) extraction method. A change from the supine to the erect position causes a change from 1500 to 1000 ml. per min. (average) in both normal and hypertensive subjects. This adjustment is prevented by splanchnic sympathectomy (79). The BSP method has been criticized by Sherlock *et al.* (80) who report spuriously high values for liver flow in man when the concentration of BSP falls below 1.0 mg. per cent. Werner & Horvath (81) have been unable to confirm this observation in the dog.

Preliminary angiographic studies by Daniel & Prichard (82) have led them to suggest the presence of a shunt mechanism within the liver similar to that described by Trueta *et al.* (83) for the kidney. A redistribution of blood to the liver and lungs during reflex responses to cold has been suggested by the angiographic studies of Glaser *et al.* (84).

The intestinal blood vessels have been studied in 340 rabbits by Hugues (85), who gives statistical data for the dimensions of the small vessels. Following hemorrhage, the arterioles constrict to 68 per cent of their control diameters. Arteriovenous anastomoses in the circulation through the stomach have been demonstrated by Walder (86), using perfusion of glass spheres. Thermal methods for estimating changes of colonic flow are described by Grayson (87), who finds evidence for vasoconstriction during fainting (88).

Skin and skeletal muscle.—Plethysmographic and calorimetric experiments by Greenfield *et al.* (89) indicate that the *proportion* of total blood flow to the hand which passes through the digits is reduced from 70 per cent to 40 per cent during the adjustment from a warm to a cool environment. Additional evidence is given (90) that plethysmographic methods are untrustworthy during cooling owing to constriction of large capacity blood vessels. Local cooling of a finger in ice water causes an intense initial constriction followed (after 5 min.) by the Lewis reaction (91) of intermittent vasodilatation producing flows as high as 30 to 100 ml. per min. per 100 ml. tissue. At the height of the Lewis reaction, the mean internal tissue temperature is 20 to

30° C. (92). The Lewis reaction has been utilized by Yoshimura & Iida (93) as a method of estimating the ability of an individual to resist exposure to cold. A "resistance index" is formulated from: (a) the mean digital skin temperature in the period 5 to 30 min. after immersion in ice-water; (b) the time of onset of the first temperature rise; and (c) the skin temperature at the time of the first rise. The "index" so obtained is a Gaussian distribution among the population of individuals tested and is said to be of practical value in assessing any given individual's general resistance to cold. Vaso-dilatation of the hand in response to radiant heat elsewhere on the body has been shown by Kerslake & Cooper (94) to be independent of blood flowing back from the heated area, thus clearly implicating a nervous pathway. Cutaneous vasomotor responses to thermal stimuli have been studied in the dog by Hemingway & Lillehei (95). The general results resemble those described for man by Landis & Gibbon (96). The mechanism of cutaneous regulation of flow by means of arteriovenous anastomoses has been questioned by van Dobben-Brockema & Dirken (97). Utilizing the Clark (98) preparation of the rabbit's ear, these workers observed that the principal vascular responses to body heating occurred in the arterioles and capillaries rather than anastomoses.

Variations of skin blood flow in response to heating or cooling of the hypothalamus in cats and dogs have been extensively investigated by Ström (99, 100). A rise in hypothalamic temperature was followed by cutaneous vasodilatation, the magnitude of which depends upon skin temperature. Vasoconstriction could be produced by electrical stimulation of the anterior hypothalamus or the frontal lobes, but was not elicited by local cooling of these regions. A preliminary account of somewhat similar experiments in chronic preparations has been given by Forster & Ferguson (101), who report that, in the unanesthetized cat, panting is primarily controlled by hypothalamic temperature, whereas cutaneous vasomotor reactions are not.

The relations between cutaneous flow and cutaneous tissue pO_2 have been investigated by Montgomery & Horwitz (102), utilizing the oxygen cathode of Davies & Brink (103). During full cutaneous vasodilatation, the pO_2 is approximately 80 per cent of that in arterial blood. However, during constriction it is reduced to one-half or one-third this value. In occlusive arterial disease, the pO_2 is low and fails to increase during administration of 100 per cent oxygen. The method has been extended by Montgomery *et al.* (104) to the study of cardiac shunts.

A plethysmographic study of blood flow and fluid exchange in skin and muscles of the human forearm has been made by Fisch *et al.* (105). It was noted that inflation of the venous occlusion cuff caused a diversion of blood from skin to muscle. Values were obtained for precapillary and postcapillary resistance to blood flow and for the mean capillary pressure at which no net fluid exchange would occur. This was estimated to be 7 mm. Hg higher than protein osmotic pressure, the difference being ascribed to tissue pressure.

The circulation in skeletal muscle has received relatively little attention

during the past year. A study has been made by Gollwitzer-Meier (106, 107) on the changes in flow and pH of venous blood from the contracting gastrocnemius of the dog. A triphasic change of pH following onset of contraction is described; this is inhibited by iodoacetic acid. Active hyperemia apparently bears no relation to the pH of the venous blood. The series of papers by Issekutz *et al.* (108, 109, 110) is also of interest in connection with the effects of metabolites on blood flow through skeletal muscle. Bean & Elwell (111) report that *d*-tubocurarine increases flow through muscle (dog); this vasodilator action is independent of innervation.

REACTIVE HYPEREMIA, TISSUE ANOXIA

The profound dilatation which accompanies the restoration of blood flow following occlusion of the circulation is one of the most striking properties of the peripheral vascular system. The current theory explaining this reaction, based principally on the work of Lewis (112) and of Krogh (113), supposes that during the period of occlusion certain unknown vasodilator metabolites are released by the ischemic tissues. Lewis postulated a histamine-like substance as the active agent. A variety of recent evidence indicates that this theory requires modification. Folkow (114) reduced the flow to skin and to muscle (anesthetized cats) by amounts insufficient to alter oxygen consumption; yet marked reactive hyperemia (RH) followed release of the partial ischemia. When the same decrease of flow was caused by a rise of venous pressure, no RH was observed. The reaction was unaffected by sympathetic or sensory denervation, acute or chronic. I have repeatedly observed this phenomenon in isolated blood-perfused hindlimbs of cats and dogs (115) during the first 10 to 60 min. of perfusion. After this time the blood vessels lose their ability for RH even though they remain responsive to histamine and other dilator agents and the oxygen consumption remains unaltered. Folkow concludes, as did Bayliss (116), that normal arteriolar tone is dependent upon intravascular pressure and that this mechanical factor is important in producing the dilatation of RH. Emmelin & Emmelin (117) and Folkow *et al.* (118) have demonstrated that RH is unaffected by drugs which abolish the response to histamine. Carlston *et al.* (119) have shown that lymph obtained from ischemic tissue has no detectable histamine-like activity and in fact is strongly histaminolytic. The possible role of potassium ion as a factor in RH has been questioned by Rewell (120) who finds no increase in blood potassium of blood from ischemic muscle and suggests that the general rise of plasma potassium following release of a limb tourniquet is due to its release from the liver. Issekutz *et al.* (109) have discovered that iodoacetate inhibits RH in muscle even though the resting oxygen consumption and lactate production are increased. In this case, the powerful vasodilator actions of acetylcholine, potassium cyanide, and nitroglycerine are also inhibited, whereas sensitivity to constrictor agents is increased. Conversely, fluoroacetate (110) is shown to enhance RH and the action of vasodilator drugs, especially acetylcholine. The possible role of acetylcholine in RH is sug-

gested by Keyssler & Schmier (121), who report that RH is diminished by atropine.

Rein has continued his complex studies (122, 123, 124) on the relation of liver and spleen to circulatory responses to anoxia. He postulates that during anoxia or exercise a substance is released from the spleen which acts on the liver to discharge a substance which increases the efficiency of the heart. He reports (125) that the active substance, "Hypoxie-Lienen" may be extracted from the spleens of anoxic dogfish. Of interest in this connection is the observation of Wayne *et al.* (126) that dogs subjected to severe hypotension (40 mm. Hg) are better able to resist shock if their livers are well perfused with blood from a donor animal during the period of hypotension. Shorr, Zweifach *et al.* (127, 128) provide further evidence that during generalized tissue anoxia initiated by hemorrhage, etc., certain vasoactive materials are released into the blood stream. Evidence is given (129) that the kidney is the principal site of "vasoexcitor" material (VEM). These materials are detected by their action in modifying the responses of the vessels of the mesoappendix to topically applied epinephrine. Methods of assay have been criticized by Wiedeman & Nicoll (130). Gordon & Flasher (131) describe a new vasoconstrictor material released into the blood from the rabbit's kidney following acute ischemia. This material has no effect on general blood pressure but produces intense blanching of the opposite kidney. Olsen & Schroeder (132) have studied renal anoxia and report a marked acidity and decreased pO_2 in cortical tissue of kidneys made ischemic by the Goldblatt procedure.

VASOMOTOR SYSTEM

Pressure receptors and chemoreceptors.—Heymans *et al.* (133) have found that activity of the pressor receptors depends greatly on the tone of the surrounding smooth muscle. Topical application to the carotid sinus area of agents known to induce contraction of smooth muscle elicits reflex vasodilation similar to that caused by a rise of pressure within the sinus lumen. Conversely, drugs known to relax smooth muscle cause reflex vasoconstriction. The effect appears to be nonspecific, depending only on the tension of the smooth muscle in the sinus wall. The effect of epinephrine is abolished by previous application of adrenolytic compounds (134). These observations may explain why the intravenous infusion of epinephrine, in amounts insufficient to cause a measurable rise of blood pressure, frequently produces reflex inhibition of sympathetic tone in extremities even when these are perfused with a separate blood supply (135, 136). They are also in agreement with the observations of Schroeder & Anschütz (137), who find in the unanesthetized dog that the reflex response to carotid occlusion is enhanced during the infusion of epinephrine. An added factor in interpreting the latter observation, however, is the increased arterial pressure caused by the infused epinephrine. As shown by Prochnik *et al.* (138), the peak reflex rise of arterial pressure in response to carotid occlusion is linearly related to the initial arterial pressure.

Jourdan & Collet (139) have discussed the effects of denervating the carotid and aortic receptors in chronic experiments. The arterial pressure rises precipitously at operation but falls to subnormal levels within 24 hr., where it is likely to remain for several days before climbing gradually to a maximum in about two weeks. The mortality is high unless the depressor nerves, rather than the vagosympathetic trunks, are severed to denervate aortic receptors. Vleeschhouwer *et al.* (140) have reinvestigated the effects of carotid occlusion on cardiac output and have failed to confirm the work of Charlier & Philippott (141), who had concluded that the cardiac output is increased under these conditions. Unnecessary confusion has arisen in this field owing, at least in part, to the short periods allowed for measurement of oxygen consumption and withdrawal of mixed venous blood. Interpretation of results would be simplified if the respiratory exchange ratio (142) were recorded to ensure the steady state conditions required for application of the Fick principle (143). An interesting new method for studying moderator activity has been described by Guyton *et al.* (144). Small amounts of blood (0.1 blood volume) are injected and withdrawn from the arterial circulation sinusoidally. The ability of the vasomotor system to prevent corresponding sinusoidal changes of arterial pressure depends, in part, upon the efficiency of the moderator reflexes. If the pressure receptors are progressively denervated, the oscillations of arterial pressure become more pronounced. Similarly, if the frequency of injection and withdrawal is increased, there comes a point at which the moderator system is unable to follow sufficiently rapidly, thus giving rise to large swings in the arterial pressure. Aviado *et al.* (145) have searched for possible new pressure or chemoreceptive areas in the heart and lungs. No new areas were found, but new evidence is given for the location of previously described areas. The results suggest that pressure-induced reflexes arise from the right atrium and proximal portion of the pulmonary artery, rather than from the great veins. Von Bezold reflexes appear to arise from the pulmonary veins. Bradycardia and peripheral vasodilation generally followed a rise of pressure in the right side of the heart, not vasopressor or cardio accelerator reflexes (Bainbridge, MacDowell).

At a symposium on chemoreceptors held in Stockholm, de Castro (146) presented his beautiful researches on the structure, innervation, and circulation of the chemoreceptor cells. Arteriovenous anastomoses within the glomus were shown to be activated by changes in composition of the blood. By an ingenious method of grafting to the chemoreceptors, nerve fibers which normally supply the afferent limb to pupillary reflexes, de Castro has been able to show that the epithelial cells are the chemosensitive elements rather than specialized nerve endings. General chemoreceptive circulatory reflexes were reviewed by Neil (147).

Electrical stimulation.—Hensel (148) has examined the effects on blood flow through hindlimbs of stimulating the lumbar sympathetic with sinusoidal currents in the frequency range 0.5 to 10 c.p.s., thereby extending the earlier work of Maltesos & Schneider (149). The threshold is fairly constant

for 10 to 3 c.p.s. but thereafter rises steeply. Folkow *et al.* (150) have investigated vasodilator reactions in the hindlimbs of cats and dogs. In all experiments reflex vasodilator reactions were abolished by sympathectomy, acute or chronic, even though the sensory nerves remained intact as detected from antidromic cutaneous vasodilatation. They conclude that dorsal root fibers do not convey centrally induced vasodilator impulses.

Electrical stimulation of the central stump of the divided vagus is said by Binet & Burnstein (151) to cause the liberation of a powerful vasoconstrictor substance into the bloodstream. This substance is not blocked by sympatholytic agents. Similar findings have been described by de la Barreda *et al.* (152), who found that the substance is still present after hypophysectomy, nephrectomy, or adrenalectomy. Jiménez Díaz *et al.* (153) found that the substance is active in plasma perfused extremities, but not in saline perfused preparations, and suggest that it may be liberated from arterial walls. Extracts from arterial walls are said to react with hypertensinogen in much the same way as does renin.

EPINEPHRINE AND NOREPINEPHRINE

The identification of norepinephrine as a humoral transmitter (von Euler, 1946) has prompted many investigations of the properties and vascular effects of norepinephrine in comparison with epinephrine. The literature up to 1950 has been reviewed by von Euler (154). The following recent additions to the field may be noted here:

Epinephrine and norepinephrine content of tissues and body fluids.—Holtz & Schümann (155, 156, 157) have found that the adrenal medulla of rabbits and guinea pigs contain mostly epinephrine in contrast to the adrenals of cats, dogs, cattle, pigs, and humans which contain variable quantities of norepinephrine. The lack of norepinephrine in rabbit adrenals has been confirmed by Hökfelt & McLean (158). In the toad, as found by Houssay *et al.* (159, 160), about 50 per cent of the total (2.5 to 5 mg. per gm.) is norepinephrine, and this ratio remains unchanged during the depletion caused by hypophysectomy. It is interesting that the adrenals of the whale also contain about 4 mg. per gm., of which 70 to 100 per cent is norepinephrine (Burn *et al.*, 161). The above data were obtained by biological assay; the chemical isolation and identification of norepinephrine from the adrenal medullas of cattle has been carried out by Bergström *et al.* (162). Norepinephrine has been identified in extracts from heart [Goodall (163)], venous blood from liver and spleen [West (164)], brain [Holtz (165)] and urine [von Euler & Hellner (166)]. Adrenal tumors contain large quantities of sympathins which may be predominantly in the form of either epinephrine or norepinephrine [Pitcairn & Youmans (167)]. The chemical state of sympathins in normal circulating blood has been investigated by Lehmann & Kinzius (168), who claim that the biological activity is less than that indicated by fluorometric procedures and suggest that epinephrine and norepinephrine may circulate partly in the form of inactive precursors.

Vascular reactions to infusion of epinephrine and norepinephrine.—In contrast to epinephrine, norepinephrine produces bradycardia in man (169). This phenomenon has been investigated in unanesthetized dogs by Lockett (170) and by Schroeder & Anschütz (137), who report that atropine blocks the cardio-inhibitory action of norepinephrine, thus implicating the buffer nerves acting via the vagi. Judson *et al.* (171) report that the cardio-inhibitory action of norepinephrine is absent in hypertensive patients. In fully denervated preparations (cat) both epinephrine and norepinephrine are cardioaccelerators (172) but only the action of norepinephrine is enhanced by cocaine. A detailed plethysmographic study of the actions of epinephrine and norepinephrine in human extremities has been conducted by de Largy *et al.* (173). Both epinephrine and norepinephrine constrict the vessels of the hand, but in muscle epinephrine is dilator, whereas norepinephrine is constrictor. When both are infused simultaneously, a ratio of five parts norepinephrine to one part epinephrine is required to balance out the opposing effects in muscle. The constrictor action of norepinephrine in human muscle has also been noted by Barnett *et al.* (174). Infusions of long duration have been carried out in rabbits by Blackett *et al.* (175). The rapid initial increase of blood pressure resulting from the infusion of norepinephrine is not long sustained. If, after eight days, the infusion is stopped, the blood pressure falls rapidly to subnormal values, where it may remain for several days. Guyton & Gillespie (176) have determined in dogs the rate of infusion of epinephrine which is just necessary to maintain blood pressure during complete spinal anesthesia—0.45 μg . per kg. per min. This might be considered as equivalent to the total normal rate of production of epinephrine, but this conclusion does not take into account the complex relations between epinephrine and norepinephrine. From the rate of rise or fall of blood pressure following the onset or termination of the infusion, it was calculated that the rate of destruction of epinephrine per minute is about two-thirds of the total amount present at any one time. In this connection Nichol & Burton (177) have noted that the destruction of epinephrine may give rise to oscillatory flow during constant pressure perfusion of the rabbit's ear with unbuffered solutions. In this case, the concentration of epinephrine reaching the arterioles depends upon the balance between the rate of supply and the rate of destruction; oscillatory flow results if each constriction reduces the supply sufficiently to allow destruction to reduce the effective concentration, thereby causing relaxation of the vessels.

Relation of epinephrine and norepinephrine to the adrenal cortex.—The vascular reactions induced by epinephrine and norepinephrine appear to be greatly influenced by adrenal cortical hormone. In adrenalectomized dogs maintained on desoxycorticosterone acetate (DCA), the response to infused norepinephrine is very much smaller than in normal animals, as shown by Ramey *et al.* (178). After a series of injections of norepinephrine, the blood vessels of the adrenalectomized dog become refractory to further injections; a single dose of adrenal cortical extract will restore their sensitivity. DCA does

not have this action. A related observation has been made by Fritz & Levine (179) utilizing the mesoappendix preparation in adrenalectomized rats. This preparation becomes refractory to topically applied norepinephrine, but the sensitivity is restored by topically applied aqueous extract from the adrenal cortex. A curious relation between epinephrine, norepinephrine, and the adrenal cortex has been noted by Meier & Bein (180). In anesthetized cats, small doses of epinephrine produce an increase of flow through the femoral artery. About 2 hr. following complete extirpation of the adrenals, however, this vasodilator action of epinephrine becomes reversed. If, at this time, traces of norepinephrine are infused ($0.002 \mu\text{g. per kg. per min.}$), the vasodilator action of epinephrine is restored. Remington (181) has noted peripheral vasodilatation in dogs about to die in adrenal insufficiency. It would be interesting to know if this vasodilatation results from failure of the sympathetic humoral transmitter to act in the absence of adrenal cortical hormone. The significance of these relations between the active principles of the adrenal medulla and the adrenal cortex is unknown and will perhaps become increasingly important to future work.

VENOUS SYSTEM, POSTURE

A comprehensive "map" of the pressures found in the superficial veins of normal supine human subjects has been published by Ochsner *et al.* (182). Large variations of pressure (e.g., 10 cm. water) may be found in any one area, but in general the pressures decrease gradually in going from periphery to heart. Henry & Gauer (183) inserted the inductance manometer (35) into a superficial vein of the foot and recorded the changes due to exercise in warm and cool environments. In a comfortable or cool environment even a slight movement suffices to reduce the venous pressure at the ankle (e.g., from 100 to 50 mm. Hg.). During the full vasodilatation of heat, however, the muscle pump is not so effective. The effects of cooling on the capacity of the peripheral veins and minute vessels is stressed by Henry (184), who shows that in the legs alone the capacity may increase from 150 ml. in the cold to 400 ml. in the warm (at 40 mm. Hg. pressure).

The effects of "negative-G" were studied by Wilkins *et al.* (185), who found that in the head-down position the vasodilator moderator reflexes acted to reduce appreciably the increment in cerebral arterial and venous pressures imposed by the increased hydrostatic pressure head. The blood pressures could be further reduced if the subjects performed the Müller maneuver or if the venous return from the legs were impeded by means of a cuff. Similar results have been found in the dog, monkey, and man by Rosenfeld & Lombard (186), but they report that goats subjected to negative-G are not able to reduce the arterial pressure as effectively as other species. Freis *et al.* (187) have shown that autonomic blocking agents and peripheral vasodilators increase the susceptibility to collapse caused by venesection or venous congestion of the extremities.

CIRCULATORY DISTRIBUTION OF SUBSTANCES, CAPILLARY EXCHANGE

Recent interest in this field has centered about the rates at which various molecular species penetrate the capillary wall and distribute to or from the tissue spaces. Tracer substances in the form of fluorescent molecules, protein conjugated dyes, radioactive atoms, and stable isotopes have been employed to study capillary exchange and distribution rates in three general ways:

Plasma clearance.—The studies of Flexner and associates on the rates at which radioactive sodium chloride (188, 189) or tagged protein (190) leave the arterial plasma of the guinea pig have been supplemented by the studies of Morel (191, 192), who has used a continuously recording and integrating circuit applied to the carotid arteries of rabbits. In general, Morel's results confirm the conclusion that arterial disappearance curves in small animals occur in the form of a simple exponential decay process. The rate constants for Na^{24}Cl and NaI^{131} were approximately the same in spite of the differences in molecular size. Similarly, Sheatz & Wilde (193) have found in rats that S^{35}O_4 and Na^{24} disappear from arterial plasma at approximately the same rate in spite of differences in charge and molecular diffusion coefficient. It is possible that these rates are determined in part by blood flow as well as by capillary permeability. For larger molecules the exponential disappearance curves may be very much slower, and perhaps limited by capillary permeability rather than by blood flow. Ferric- β_1 -globulin (190), iodinated casein (192), and albumin (194) have been investigated from this point of view; appreciable quantities of tagged albumin appear in the lymph a few minutes after its introduction into the circulation [Wasserman & Mayerson (194)].

The interpretation of arterial disappearance curves in terms of capillary exchange is complicated by the observations of Pappenheimer *et al.* (195) and Schloerb *et al.* (196), who have demonstrated that there is a large arteriovenous concentration difference which decreases exponentially with time throughout the distribution process. This invalidates the assumption made by Flexner, Morel, and others that the arterial concentration is equal to the mean capillary concentration of the test molecules, and leads to the conclusion that the capillary exchange rate of small molecules such as sodium chloride is about a hundredfold greater than previously supposed.

Tissue clearances.—The possibility of estimating effective tissue blood flow, or capillary exchange rates, or both, from the rate at which tracer molecules are removed from a given tissue has been discussed by Kety (197, 198). Preliminary data were given for the exponential rate at which Na^{24}Cl is cleared from the gastrocnemius muscle following a single intramuscular injection. The clearance was found to be about 5 per cent per minute in normal subjects; it decreased to 1 per cent during local vasoconstriction produced by epinephrine and to 0 during occlusion of the circulation. Values as high as 10 to 15 per cent were obtained during reactive or active hyperemia. These experiments have been repeated and confirmed by Wisham *et al.* (199)

and by H. Miller & Wilson (200), but Semple *et al.* (201) were unable to obtain consistent results. Stone & W. Miller (202) have compared the amount of Na^{24}Cl disappearing from the site of injection with the amount recoverable from lymph and venous blood draining the area. No appreciable quantity was found in lymph, but good recoveries were obtained from the venous blood. The authors do not comment on the fact that their data show no correlation between blood flow and exponential clearance rate; indeed, the lowest flow rate was associated with the highest clearance rate. Hyman *et al.* (203) report preliminary studies on the differential rates at which tracer molecules are taken up from the muscles. The concentration ratio of $\text{Na}^{24}/\text{I}^{131}$ or $\text{I}^{131}/\text{P}^{32}\text{O}_4$, etc., is evidently not the same in venous blood as in the injection fluid, a fact which suggests that tissue clearance depends upon diffusion as well as upon tissue blood flow. A method for estimating the tissue concentration of injected tracer materials in which conductivity rather than radioactivity is employed has been described by Birchall *et al.* (204).

A review of tissue clearances (and uptakes) of inert gases has been published by Jones (205). In general the rates at which inert gases (nitrogen, krypton, argon, etc.) exchange with the tissues is limited by the effective blood flow, rather than by capillary permeability. This is almost certainly a result of their lipid solubility, since Renkin (206) has shown that lipid-soluble molecules in general diffuse very much more rapidly through capillary membranes than do lipid-insoluble molecules of comparable size and diffusion coefficient. This observation suggests that tracer substances having high partition coefficients between oil and water might be employed in future work relating tissue clearance to blood flow.

Tissue uptake.—Schiller (207) has studied factors affecting the development and duration of fluorescence in the abdominal skin of the rabbit following intravenous injection of fluorescein. The development of fluorescence is greatly retarded by epinephrine or by rutin but only the former is inhibited by Dibenamine (N, N-dibenzyl- β -chloroethylamine). The effects of rutin, and presumably of other vitamin P flavonoids, are ascribed to vasoconstriction rather than to changes of capillary permeability. A similar conclusion has been reached by Crismon *et al.* (208), who found that rutin decreases the threshold for epinephrine and antagonizes VDM in the rat's mesoappendix preparation. The rate of accumulation of P^{32}O_4 in the gastrocnemius muscle of the rat following intraperitoneal injection of the tracer has been determined by Gilbert *et al.* (209). Uptake in the muscle was delayed during maximal tetanic contraction, presumably because the blood flow was impeded.

Exchange between parabiotic rats.—A specialized but fascinating case of circulatory and capillary exchange has been described in a series of papers by Van Dyke, Li, Evans, and their associates, who have measured the exchange between parabiotic rats and utilized the results to estimate the distribution and life-span of growth hormone, adrenocorticotrophic hormone (ACTH) and other components of the blood. The development of a method for determining

the exchange rate of whole blood between parabionts was first carried out by Huff *et al.* (210) utilizing Fe^{59} tagged red cells. The results showed that approximately 40 per cent of the blood volume exchanged per hour. A detailed mathematical treatment of factors governing exchange across the parabiotic barrier will be found in this paper. The results and theory were then applied to the case where one or both parabionts were hypophysectomized and the activity of either natural or injected pituitary hormones was determined in each animal [Van Dyke *et al.* (211)]. The distribution volume of growth hormone was found to be 28 per cent of the body weight with a life span of 9 hr., in contrast to ACTH which distributed rapidly into 43 per cent of the body weight and had a life span of only 17 min. The clearance of injected ACTH from the plasma had a half time of only 5.5 min. [Greenspan *et al.* (212)]—not much less than that for Na^{24} or S^{35}O_4 in the rat (193). The same principles have been applied by Van Dyke and Huff (213) for determining the life span of white cells; the average life of mononuclear leucocytes was found to be 170 min., that of polymorphs to be only 23 min.

HYPERTENSION

Circulating humoral agents, arterial constriction.—A pressor substance—"Pherentasin" has been extracted from the blood of patients with renal hypertension by Schroeder & Olsen (214). Purification of this agent [Olsen & Schroeder (215)] indicates that it is of low molecular weight, alcohol soluble, and extractable into organic solvents from alkaline solution. It is rarely found in normal blood or in blood from patients with neurogenic or malignant hypertension.

Constriction of large arteries has been noted by de Scoville (216) in an angiographic study of experimental renal hypertension in the rabbit. Evidence from photographs showing intense constriction of the femoral artery is supplemented by direct measurements of arterial diameter in autopsy material. The constriction appears to be greatest on the side of the ischemic kidney. Asteroth & Kreunziger (217) have studied the distensibility of the carotid sinus region in necropsy material taken from patients who suffered from various forms of hypertension. They report that the distensibility is greatly reduced in carotid sinuses from essential or malignant hypertensives, but is "normal" in renal hypertensives. This would favor Volhard's theory of neurogenic hypertension but is hard to reconcile with the recent observation of Heymans *et al.* (133) that increased tone of the carotid sinus region leads to reflex dilatation. Lee & Holze (218) report that constriction of the meta-arterioles may be observed in the conjunctival circulation of hypertensives. The sensitivity of these vessels to topically applied epinephrine is increased.

Renal hypertension and sodium.—Dole *et al.* (219) have completed a careful study of the effects of restricting dietary sodium chloride on the blood pressures of five hypertensive patients who were kept under supervision on the ward for 6 months. Following restriction of sodium chloride intake from 180 m.eq. per day during the control period to 7 m.eq. per day, all the pa-

tients lost 15 to 20 per cent of their total body sodium and experienced a reduction of blood pressure. The patients did not lose water equivalent to the amount of sodium lost, and since the plasma concentration remained unaltered it was inferred that the cells of the body became more hydrated. Clinical studies of sodium chloride restriction in hypertension have been carried out by Corcoran *et al.* (220) and by Kopperman (221). The latter believes that the reduction of blood pressure during restriction of sodium chloride is a result of a diminished cardiac output, but the methods employed to determine cardiac output (Wezler-Boger) are extremely dubious as emphasized by Grosse-Brockhoff & Kaiser (222). Tosteson *et al.* (223) have continued studies on the intake of sodium selected by rats with severe hypertension induced by encapsulation of both kidneys with latex envelopes. Hypertensive rats choose to ingest less sodium than controls; this preference is maintained following adrenalectomy, administration of DCA or during increased fluid intake engendered by diluting the (milk) diet. The factors responsible for the diminished voluntary intake of sodium by hypertensive rats remain unknown.

The production of hypertension in rats by forcing them to drink hypertonic sodium chloride is reported by Sapirstein *et al.* (224). The hypertension so produced is moderate, leading to systolic pressures in the range 150 to 160 mm. Hg; it persists so long as the sodium chloride regime is continued. Subsequent studies by Brandt *et al.* (225) show that the salt hypertension persists at least four weeks after adrenalectomy; it persists after nephrectomy until the animal dies.

Circulating humoral agents, arterial constriction.—For other papers dealing with peripheral blood flow in experimental hypertension see also pages (348–52) of this volume.

Lipids, lipoprotein, atherosclerosis.—Davidson *et al.* (226) have examined the relations between dietary choline and atherosclerosis in the dog. Contrary to previous reports, no evidence was found to indicate that choline affects the concentration of plasma cholesterol or phospholipid or that it protects against the development of arteriosclerosis in animals fed large quantities of cholesterol. Similar conclusions were reached by Firstbrook (227), using rabbits, and Stamler *et al.* (228), using chickens. Rats fed a choline-deficient diet do not develop hypertension (229). However, weanling rats may suffer severe renal damage as a result of a brief period of choline deficiency and then go on to develop renal hypertension as shown by Hartroft & Best (230) and by Moses *et al.* (231).

A new aspect of hypertension as it relates to blood lipids has been described in several articles by Gofman and associates (232, 233, 234). These workers report the presence in plasma of a lipoprotein of high molecular weight (approximately 3,000,000) which may be detected and analyzed in the ultracentrifuge. Its concentration in plasma appears to correlate fairly well with dietary intake of cholesterol and with the development of atherosclerotic lesions. This is in contrast to chemically analyzed plasma lipid or

cholesterol which often bears little relation to the severity of the sclerosis. The analysis of this lipoprotein has so far been conducted only from ultracentrifuge data and its relation to previously described lipoproteins is as yet unknown.

Metabolism of the arterial wall.—The possibility that the metabolism of the arterial wall may play a role in hypertension has been raised by Siperstein *et al.* (235), who report that arterial slices are capable of synthesizing cholesterol from acetate. Lansing *et al.* (236) give detailed data for the amino-acid composition of arterial tissue; they find an increase in the number of dicarboxylic acids with increasing age which may account for binding of calcium. Histological changes similar to those of age have been induced in young rats by x-radiation [Smith & Lowenthal (237)].

EXPERIMENTAL HEMORRHAGE AND TRANSFUSION

The circulatory adjustments of dogs to massive transfusions of whole blood have been studied by Guyton *et al.* (238, 239). Very large quantities of blood, up to 2.5 times the normal blood volume, may be introduced intra-arterially without causing much change of blood pressure provided that the transfusion rate is slow (e.g., less than 0.1 blood vol. per min.). At high rates of transfusion (e.g. 1 blood vol. per min.) both arterial and venous pressures rise precipitously. When transfusion stops, the pressures fall exponentially with a half-time of about 3 min. The half-time is unaffected by denervation of the pressure receptors or by spinal anesthesia. Most surprising is the finding that the total plasma protein of the recipient remains unchanged, indicating that an amount of protein equal to that transfused must leave the circulation within a few minutes. This finding, if substantiated, poses a new problem in capillary permeability.

The role of the sympathetic nervous system in the development of experimental hemorrhagic shock in dogs has been investigated by Wiggers *et al.* (240). Small doses of Dibenamine, enough for partial inhibition of peripheral vasoconstrictor tone, were effective in preventing the onset of irreversible shock. This would support the theory expressed by Shorr *et al.* (127) that prolonged peripheral vasoconstriction leads to the production of vasodepressor materials and irreversible shock. A potential factor in producing vasoconstriction following hemorrhage which has not previously been considered has been described by Kenny & Neil (241). In cats and dogs the chemoreceptors are apparently activated as a result of hemorrhage, as indicated by a further fall of blood pressure when the chemoreceptor impulses are blocked. Supplementary evidence from recording of action potentials from chemoreceptor areas during hemorrhage has been noted by Landgren & Neil (242). Possibly the AV anastomoses within the carotid and aortic bodies (146) may be involved in this response.

Blood flow through the kidneys following repeated hemorrhages of severity sufficient to produce chronic anemia has been investigated by Paterson (243) and by Netravisesch & White (244). Renal blood flow as calculated

from C_{PAH} and hematocrit is reduced under these conditions, despite decreased viscosity, thus indicating over-all renal vasoconstriction. However, filtration rate remains relatively unaffected as in hypervolemia or polycythemia (62). No indications are given as to whether this renal vasoconstriction is autonomous or whether it occurs as part of the general vasoconstrictor response to hemorrhage. Circulatory responses to transfusion of the carbohydrate polymer, dextran, periston (polyvinylpyrrolidone), and other polymers of high effective osmotic pressure are being studied in numerous laboratories. Preliminary reports of interest have appeared (245 to 248), but no detailed accounts of physiological investigations employing well-characterized monodisperse polymers have yet been published.

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During the period to be covered by this review international congresses in physiology and in cardiology have taken place. In the focus of general interest have prevailed investigations concerning, *inter alia*, metabolic aspects of cardiac activity, cardiac failure, and arteriosclerosis, hemodynamics of the pulmonary circulation, three-dimensional electrocardiography, and the extension of cardiac surgery to acquired valvular heart disease. Physiology and pathophysiology of the heart, thus, on the one hand is in the process of being linked up with recent progress in biochemistry and on the other hand has profited by technical refinements of instruments for clinical research. Only few of the communications will be quoted here; the reader is referred to the collections of abstracts (1, 2).

CARDIAC MUSCLE

Metabolism.—Different aspects of normal heart muscle metabolism have been reviewed by Engström (3), Biörck (4), and Snellman (5). Edman (6) in studies on the action of ouabain on myosin-bound adenosinetriphosphatase found distinct differences between cattle heart muscle extracts and preparations of washed actomyosin. Wollenberger (7, 8) continued his investigations into cardiac metabolism, regarding the effect of succinate upon the adenosinetriphosphate content of the dog heart as well as the influence of glycosides upon isotope-labeled glucose metabolism. Goodale *et al.* (9) in mildly diabetic patients found abnormal patterns of heart muscle metabolism. Insulin promoted the phosphorylation not only of glucose but also of pyruvate and apparently induced a nonoxidative utilization of the glucose. Determinations of cytochrome-*c* in human hearts were reported by Biörck (10), and the possibilities of therapeutic administration of respiratory catalysts in hypoxic conditions were discussed.

Schmidt *et al.* (11) found a striking excess of nonprotein nitrogen substances in heart muscle as compared to skeletal muscle. Electrolyte and water contents of cardiac and skeletal muscle in normal hearts and in conditions of ventricular hypertrophy and infarction were investigated by Alexander *et al.* (12). Normal values were given. The authors confirm earlier studies indicating a reduction in potassium content of both cardiac and skeletal muscle in decompensation and digitalization. Whereas most electrolytes were reduced in the recently infarcted myocardium, sodium and chloride were significantly increased. Goodall (13) in beef heart extracts found epinephrine, norepinephrine, and an unknown sympatholytic factor, that had an

¹ The survey of the literature pertaining to this review was concluded in June, 1951.

² I am indebted to Mrs. Inga Winnerstam for her assistance in collecting material for this review.

inhibiting effect upon the aforementioned substances. This factor seems to be specific for the heart, as it could not be detected in spleen or adrenal extracts. Penrod (14) investigated cardiac oxygenation during severe hypothermia in the dog and found no serious cardiac hypoxia to result from the leftward shift of the hemoglobin dissociation curve at 20° C. Bigelow *et al.* (15, 16) attempted to utilize general hypothermia to overcome difficulties in cardiac surgery. Though as yet not very encouraging, their results are of considerable interest. The metabolism of rat heart slices under various conditions of anoxia and temperature was determined by Fuhrman *et al.* (17). Rein (18) extended earlier studies on a water-soluble substance which is released by the spleen during conditions of hypoxia and, after activation in the liver, may increase the efficiency of the myocardium.

A most stimulating survey of myocardial metabolism in congestive heart failure was presented by Olson & Schwartz (19). Bing *et al.* (20) in a study on 80 patients by means of coronary sinus catheterization and the nitrous oxide method for coronary flow found an increase in initial tension of heart muscle fibers to augment myocardial oxygen metabolism, which, however, again decreased when the patient was in failure. This probably reflects a defective conversion of oxidative energy into useful work. Strophanthus preparations given intravenously aided in this conversion in failing hearts, but caused a reduction in the output of the normal heart (21). Related problems were studied by Page *et al.* (22) on dogs. They also found a decrease in cardiac output together with a decrease in coronary flow. As mean arterial blood pressure rose, the authors, however, conclude that mechanical efficiency was maintained better than without ouabain. Webb *et al.* (23) related the pharmacological action of quinidine to an observed depression of the cardiac oxidative metabolism.

The vast number of publications concerning the influence of adrenocorticotrophic hormone and cortisone on mesenchymal tissue deserve careful consideration from all cardiologists, but cannot, because of lack of space, be reviewed here.

Coronary circulation.—Gregg *et al.* (24) compared values for coronary blood flow determined by the nitrous oxide method with those obtained by a direct method using the rotameter and found a considerable difference, amounting to between +21 and -22 per cent, with an average variation of ± 12.4 per cent. Factors in the variation and regulation of coronary circulation in intact anesthetized dogs as measured by the nitrous oxide method were discussed by Foltz *et al.* (25) who believe that multiple mechanisms, but particularly cardiac oxygen metabolism, influence the distribution of coronary blood flow. Ramos *et al.* (26, 27) reinvestigated extravascular and nervous influences on coronary circulation in perfused dog hearts and arrived at the conclusion that the vasomotor innervation of the coronary vessels did not differ from that of other vessels in the organism. Eckstein *et al.* (28) studied the effects of controlled cardiac work upon coronary flow and myocardial oxygen consumption after accelerator nerve stimulation. The increase in oxygen consumption and coronary flow far outweighed the in-

crease in work, thus rendering the heart anoxic and inefficient. The effect of intravenous aminophylline upon coronary blood-oxygen exchange was investigated by Foltz *et al.* (29) by coronary sinus catheterization and the nitrous oxide method in anesthetized dogs. They found that aminophylline increased the demands for myocardial oxygenation but did not assist in providing the necessary oxygen. There was, therefore, an increase in the arterio-venous oxygen difference. In contrast, nitroglycerine raised the oxygen saturation of coronary venous blood during the phase of maximal depression of blood pressure. Eckstein *et al.* (30) found no change in myocardial oxygen consumption after nitroglycerine. The effect of nitroglycerine on the cardiovascular system of normal persons was found by Wégria *et al.* (31) to be a rise in cardiac output without change in blood pressure and thus an increase in cardiac work.

Different responses of coronary vessels to epinephrine and posterior pituitary extracts in isolated hearts of cat and rabbit were reported by Kordik (32). Lu & Melville (33) found both coronary constriction and dilatation after norepinephrine. Chambliss *et al.* (34) found that red blood cells on hemolysis released a substance which exerted a potent dilating influence upon coronary vessels in dogs. They consider most probable that the substance is adenosinetriphosphate or some related compound.

Rein (35) investigated the mechanism of adaptation of the coronary vascular bed to mechanical strangulation. Sayen *et al.* (36) studied local oxygen availability in dog hearts with experimental infarctions and claim a definite beneficial effect of pure oxygen inhalation in order to reduce the injured area. The problem of revascularization of the heart by anastomosis operations on the coronary vessels was discussed by Johns *et al.* (37) and by McAllister *et al.* (38).

Coronary arteriosclerosis.—Closely connected with the study of the coronary circulation in man are recent investigations that seem to offer dependable evidence regarding the role of cholesterol and related lipids in the genesis of that great menace to mankind, coronary arteriosclerosis. Yater *et al.* (39) have investigated the relationship between clinical and pathological aspects of 950 cases of coronary artery disease subjected to necropsy. Geiringer (40) found that one of every five anterior descending coronary arteries in man runs for all or part of its course in the myocardium. In such arteries intima and media are comparatively thin and rarely develop atherosclerosis. Positive evidence of an age-relationship for total serum cholesterol values was reported by Keys *et al.* (41) and by Gertler *et al.* (42) who also found the ratio between cholesterol and phospholipids to be particularly important in the diagnosis of coronary artery disease. The connection between coronary heart disease and elevated serum uric acid was stressed by Gertler *et al.* (43) and its relation to gout by Ask-Upmark & Adner (44). Gertler *et al.* (45) found no definite relation between ingested cholesterol and serum cholesterol, and they question the rationality of low cholesterol diets. Gofman *et al.* (46), however, in fundamental studies with ultracentrifuge methods, have broken up serum lipids in several fractions according to Svedberg units

and found a certain class of molecules not related to total serum cholesterol levels, but definitely related to atherosclerosis and amenable to decrease by dietary restrictions of fat and cholesterol over a period of weeks to months. If this is further confirmed, it may help to explain the surprising fact that dietary restrictions during wartime caused an almost immediate reduction in death from atherosclerotic heart disease. A preponderance of big fat particles observed under dark field illumination in serum from atherosclerotic patients as compared to that of normals was reported by Zinn & Griffith (47). Experimental atherosclerosis in the chicken has been extensively studied by Katz and co-workers (48 to 52). Atherosclerosis was induced by cholesterol feeding or stilbestrol implantation. Within limits this atherosclerosis was reversible. Thyroid hormone retarded the development of induced atherosclerosis but not of the spontaneous form; low fat diets retarded the spontaneous lesion but did not affect the induced one. Depancreatization made the lesion more severe; choline and inositol were without prophylactic effect. Hall *et al.* (53) reported that ammonium chloride did not protect rats receiving desoxycorticosterone acetate from hypertension, but it seemed to be effective in moderating the severity of the vascular damage which follows sustained hypertension.

CARDIAC ACTIVITY; METHODS OF STUDY

Electrocardiography.—Comprehensive surveys of the present status of clinical electrocardiography have been given (54, 55). In a monograph (56), Schaefer has attempted to unite electrophysiological and clinical interpretations of the electrocardiogram. Basic principles in the interpretation of electrocardiographic findings were, however, challenged by Benjamin *et al.* (57) regarding the homogeneity of electrical fields in living tissue and by Robb (58, 59) relative to polarity patterns in unipolar leads and their relation to fiber direction versus anatomic topography. Simonson *et al.* (60) supported Duchosal & Sulzer's hypothesis that every lead reflects a central vector and not merely local patterns. A new direct-writing electrocardiograph with a flat frequency response up to 1,000 c.p.s. was presented by Elmquist (61).

Most papers in this field were concerned with unipolar leads, vectocardiography, and intracavity electrocardiography. There is a strong tendency towards realization of practical procedures for three-dimensional electrocardiography. The original paper by Einthoven and his co-workers on the direction and manifest size of potential variations and influence of position in the human heart was translated into English (62). Cronvich *et al.* (63, 64) investigated standardizing factors to correlate measurements in any given coordinate reference frame employed in electrocardiography, and McFee (65) investigated the errors in manifest vectors from inaccurate measurement of voltage. Fowler & Braunstein (66) found good correspondence between electrical and anatomic position of the heart except for rotation about the transverse axis. Schaefer (67) questioned the validity of the explanation of the "intrinsic deflection" in unipolar lead electrocardiography.

raphy. Herrmann *et al.* (68) in a study on 200 cases claimed the superiority of Wilson leads to other chest leads and was supported in this view by Kistin & Brill (69). The use of Wilson leads and augmented limb leads was also recommended by Rosenman *et al.* (70) and by Sokolow (71), while Fiske (72) considered the unipolar limb leads of little additional value in the diagnosis of myocardial infarction. Lian *et al.* (73) studied serial bipolar chest leads on dogs and believe this procedure to give valuable information.

Johnston *et al.* (74) have described an electronic circuit capable of integrating the electrocardiogram and measuring the net areas of its various waves. Vectocardiographs were presented by Briller (75), Becking (76), Grisham (77), Kaindl (78) and their co-workers. A method of calculating spatial vectors of the heart from conventional leads was reported by Grant *et al.* (79, 80). Millot (81) Meyer & Herr (82), and Jouve *et al.* (83) discussed three-dimensional electrocardiography and the ventricular gradient, while Koechlin (84) summarized the conclusions of the Paris congress in these matters.

Attempts to utilize new locations of the different electrode have continued. Such studies include: data on normal esophageal (85, 86) and gastric (85) electrocardiograms, displacement of the RS-T segment during induced anoxia, and digitalization in such leads (87, 88), and intrabronchial electrocardiography (89, 90, 91).

Potential variations from the endocardial surfaces, recorded during cardiac catheterization, have continued to attract interest. Kossmann *et al.* (92) studied simultaneous records from the right heart and attached vessels in relation to conventional electrocardiograms. Other studies concern intra-atrial potentials (93) and the basis of the asynchronism in impulse formation between right and left atria (94). Zimmerman & Hellerstein (95), Sodi-Palares *et al.* (96), and Steinberg *et al.* (97) have studied the cavity potentials of the left ventricle, the latter authors also obtaining simultaneous records from both ventricles, while bipolar endocardial studies on the order of excitation of the ventricular myocardium were performed by Duchosal *et al.* (98). It is apparent that left heart catheterization in man is not a safe procedure. Hueber & Wohlrab (99) claimed that unipolar leads in the supraclavicular region will pick up cavity potentials and thus give valid information regarding the electric state of subendocardial layers.

Electrocardiographic tolerance tests for coronary insufficiency have been further investigated by Nylin *et al.* (100), who on the basis of 1,130 hypoxemia tests were able to verify Björck's earlier results. Björck & Dalhamn (101) investigated the prognostic value of such tests in a seven-year follow-up and concluded that among males the mortality was higher in the group with positive tests than in the negative group. Peter (102) denied the usefulness of sympatholytic substances in differentiating functional and organic coronary insufficiency, but the evidence presented is hardly convincing. Stein & Weinstein (103) continued their studies on the use of ergonovine as a test for coronary heart disease. In as much as one of their criteria of a positive test is the subjective feeling of pain, the test cannot be considered as an objective

method. Effort tests were discussed by Wood *et al.* (104) and by Sjöstrand (105). Jacobs (106) studied the relative merits of the Ivy-Krasno nitroglycerine flicker fusion test (107) as compared with the two-step exercise test. Hendley (108) confirmed the effect of vasomotor drugs on flicker fusion frequency.

Ballistocardiography.—After years of trials, ballistocardiography now seems to offer much-improved possibilities for the study of cardiac output as indicated by studies by Brown & de Lalla (109), Nickerson (110), Jones & Goulder (111), and de Lalla *et al.* (112). Criticism of Starr's output formula was expressed by Galdston & Steele (113). Changes in the ballistocardiogram relative to respiration were described by de Lalla & Brown (114) and, after exercise, by Makinson (115) and Mathers *et al.* (116). Coronary artery disease patterns were investigated by means of a simplified electromagnetic ballistocardiograph by Mandelbaum & Mandelbaum (117). Ballistocardiographic vectors were analyzed by Scarborough *et al.* (118).

Elektrokymography.—Elektrokymography has continued to attract wide attention. Recent studies concerned the fidelity of elektrokymographic records (119), the normal cardiac cycle (120, 121), the effect of positional changes (122), and the correlation of simultaneously recorded elektrokymograms and pressure pulses (123). Other reports dealt with the elektrokymogram of the left ventricle (124), the left atrium (125), the right atrium (126), constrictive pericarditis (127), and coarctation of the aorta (128). Eddleman *et al.* (129) used the elektrokymograph to investigate digitalis action upon stroke volume and cardiac cycle in normal subjects. Rudel (130) studied the pulmonary densogram in dogs and found that volume increase and pressure rise, as determined by catheterization, do not parallel each other.

Angiocardiography.—Angiocardiography and aortography were also extensively studied. General surveys were given by Scott (131) and Morgan (132). Possible dangers continue to be investigated. Various groups (133, 134, 135) have discussed the electrocardiograms of patients with angiographic evidence of myocardial damage, while Gordon *et al.* (136) investigated the cardiovascular effects of injected Diodrast (iodopyracet) and found vasodilatation to be most significant and hard to prevent, even at slow injection rates. Axén & Lind (137) studied spatial and temporal relations between electro- and angiocardiographic recordings. Dotter *et al.* (138) studied aortic length by means of angiocardiography. Ponsdomenech & Nunez (139, 140) performed heart puncture in man for Diodrast visualization of the ventricles and claim that they had no accidents in 45 examinations.

Cardiac catheterization.—Recent technical contributions include: an electronic apparatus for pressure measurements (141), a new technique of differential pressure measurements using condenser manometers (142), the evaluation of an intracardiac manometer (143), a preliminary report of a method of magnetic guidance of a catheter with articulated steel tip (144), and instruments for continuous determination of the oxygen percentage in air using the paramagnetism of oxygen (145, 146).

Griffin *et al.* (147) studied the variability of direct Fick values and the reliability of right atrial blood samples in determining cardiac output in

dogs and found that, with correct positioning of the catheter, right atrial samples were as good as those drawn from the pulmonary artery. Puncture of the right ventricle under fluoroscopic guidance instead of catheterization was used in dogs by Formel *et al.* (148).

Other methods.—Several studies deal with attempts to avoid the cumbersome gas analysis for the calculation of cardiac output by the Fick principle. Most reports concern photoelectric recordings of injected dye (149 to 153). Also pertinent in this connection is Penneys' opinion (154) that a correction for ear thickness should be employed in the use of Millikan's oximeter. Sleator *et al.* (155) presented an oximetric method for cardiac output determination without introduction of dye, and Grossman & Weston (156) claimed that cardiac output could be determined by injection of a test substance like *p*-aminohippurate through the distal lumen of a double lumen catheter into the pulmonary artery and sampling of blood from the proximal lumen in the right ventricle. It may be true that some of these methods, if sufficiently accurate, will give as much information about the residual blood volume of the heart as of variations in cardiac output.

Other studies in this field include: a method for continuous recording of cardiac output in the anesthetized animal by means of an electromagnetic rotameter (157), comparison of stroke volume determined in dogs by means of a rotameter and by means of the pressure pulse contour method (158), and the usefulness of the physical method of determining cardiac output by the method of Wezler-Broemser (159).

ELECTRICAL EXPRESSION OF CARDIAC ACTIVITY

Excitability.—Luyet (160) described rapid cooling to -195°C . and rapid rewarming of chick embryos with preservation, after rewarming, of spontaneous rhythmic cardiac contractions. Delaunay *et al.* (161, 162, 163) and von Bonsdorff (164) studied action currents in tissue cultures of fragments of embryonic chick hearts and found them remarkably similar to ordinary electrocardiograms. Reversible inhibition of contractions in such tissue cultures by desoxycorticosterone acetate was reported by Cornman (165).

The functional structure of cardiac muscle in electrophysiological elements was discussed by Rothsuh (166) and by Kisch (167), and a comparison of embryonic and adult heart muscle physiology was made by von Tschermak-Seysenegg (168). Other contributions in this field include: resting membrane and action potentials of single fibers from frog heart (169), excitability and refractory period in isolated heart muscle of cat (170), the separability of contractile force and irritability in cat heart muscle (171), the process of excitation in the myocardium of dog (172, 173), and the excitation of the human atrial muscle with special reference to the intrinsic deflection of the atrial component (174). Another series of papers by Orias *et al.* (175 to 178) also deal with the excitability of mammalian atrium and ventricle. Trautwein (179, 181, 182) and Schaefer (180) likewise investigated the changes in excitability secondary to cardiac insufficiency and its treatment with strophanthin.

The influence of certain drugs on the irritability and automaticity of

heart muscle was further studied by Greiner & Garb (183). Farah & Loomis (184) found digitalis to act upon the atrium two opposite ways: one direct, increasing its refractoriness and decreasing its conductivity, the other by reflex vagal action with opposite effect. The net result upon atrial activity thus depends upon the relative magnitude of each component.

Relation of the electrocardiogram to the general bodily state.—Data were presented concerning the electrocardiograms of premature infants (185), unipolar leads in healthy infants and children (186, 187), chest leads in 100 healthy adults (188), and the change in electrical axis from birth to old age in 600 healthy persons (189). The diagnostic and prognostic importance of prolongation of Q-T intervals in acute myocarditis of rheumatic and nonrheumatic origin was discussed by Gittleman *et al.* (190), by Taran & Szilagyi (191), and by Dreyfuss & Diengott (192), while normal Q-T values were found in chronic cor pulmonale by Alexander *et al.* (193). The relationship of the electrocardiogram to type of lesion and to prognosis was studied in atrial flutter by Hejtmancik *et al.* (194), and in bundle branch block by Shreenivas *et al.* (195, 196, 197) and Rodstein *et al.* (198). Schaefer & Doerner (199) discussed T wave analysis in general, and Doerner applied their views in a study of the origin of T wave changes in valvular heart disease and in hypertension (200, 201). The electrocardiogram of patchy myocardial fibrosis was studied by Weinberg *et al.* (202). Marked T wave changes were found in five siblings with Friedreich's ataxia by Lorenz *et al.* (203). The electrocardiographic abnormalities of dystrophia myotonica were studied by de Wind & Jones (204) and by Fisch (205), while the heart in progressive muscular dystrophy was the subject of a study by Zatuchni *et al.* (206). It is obvious that heart muscle often is involved in these conditions, which points to a common humoral or metabolic etiology, in the elucidation of which cardiac investigations might be increasingly helpful.

Conductivity.—Studies on the atrioventricular conducting system of the heart of the dog (207, 208) and of the ox (209) have been reported. Geppert & Schaefer (210) investigated the relationship between the size of the heart and the potential of the QRS deflection and found high voltage in hypertrophy but decreased voltage in dilatation. Postural changes in the electrocardiogram after myocardial infarction were studied by Brofman *et al.* (211), who concluded that posterior infarctions which were otherwise masked might be revealed by changes in posture. Other studies in this field include: changes in ventricular gradient in orthostatic electrocardiograms (212), the effect of a single inspiration in lead III and CF IV (213), and striking P wave vector changes in Valsalva's experiment (214).

The diagnostic value of the electrocardiogram in congenital heart disease was discussed by Bayer & Ganter (215) and by Uhley (216). The importance of unipolar leads in this connection was stressed by Sokolow & Edgar (217) and by Weissel (218). Grishman *et al.* (219, 220) discussed the nature of left axis deviation in congenital lesions with right ventricular hypertrophy. The natural history of the electrocardiogram in mitral stenosis in cases followed over a long period was discussed by Carouso *et al.* (221) and by Rasnussen

& Bøe (222), who believe dilatation of the right ventricle to be the most important basis of the observed changes. Further studies in this field include: the electrophathology of acute cor pulmonale (223), the electrocardiogram of pulmonary embolism (224), that of right ventricular hypertrophy (225, 226), and that of left ventricular hypertrophy (227, 228), also by means of esophageal leads (229). The importance of the transition zone in precordial leads in evaluating strain patterns was minimized by Rosenman *et al.* (230, 231).

The interpretation of electrocardiographic pictures commonly referred to as "bundle branch block" is again the subject of controversy. A method for production of septal lesions was described by Taylor *et al.* (232). Sodi-Pallares *et al.* studied intracavity leads in bundle branch block (233) and the sequence of activation within the interventricular septum in dogs (234) and arrived at the conclusion that activation proceeds from below upward and that retardation in bundle branch block takes place in a very limited region close to the right surface of the septum. Segers (235), on the contrary, believed the correct interpretation of bundle branch block to be that of a block between the Purkinje cells and the cardiac muscle proper. Rosenman *et al.* (236, 237) after a comprehensive discussion of the subject proposed that the term "bundle branch block" be replaced by the term "intraventricular block," since this would include the former lesion as well as defective impulse transmission in the free walls of the ventricles. Though this is at present may be convenient for the clinician, it will not help in clarifying the mechanisms. Here is an essential problem, as is also shown by the paper of Myers (238) on the resemblance of myocardial infarction and bundle branch block in precordial leads, by that of Laham *et al.* (239) on the diagnosis of ventricular hypertrophy in patients with bundle branch block, and by that of Scherlis & Grishman (240) on spatial vectocardiography. Vectocardiograms (241) and electrokymograms (242) in intraventricular blocks were further studied by Segers *et al.*, while Schwedel *et al.* (243) on the basis of an electrokymographic study of abnormal left ventricular pulsations, believed this method might aid in the diagnosis of myocardial infarction in the presence of left bundle branch block.

Transitory disturbances of the electrocardiogram simulating the picture of coronary insufficiency were described by Segers *et al.* (244), and by von Ahn (245). Dowling & Hellerstein (246) reinvestigated the influence of drinking iced water on the T wave vector and found ventricular gradient changes to depend upon delayed repolarization of the posterior heart wall. Lepeschkin (247) arrived at the conclusion that the T wave and ventricular gradient depend on temperature differences between subendocardial and subepicardial parts of the myocardium of the apex region. T waves of electrograms from fetal heart muscle were studied by Groedel & Miller (248) and from papillary muscle of the cat by Garb (249). Koelbing (250) studied the T vector after digitalis and arrived at the conclusion that such T wave changes are independent of the autonomic nervous system. Levine *et al.* (251) maintained that they are due to delayed repolarization of the apical fibers. Liebow & Hellerstein (252) found acetylcholine to influence myocar-

dial repolarization. Sjöstrand (253, 254) investigated the influence of heart rate upon S-T and T and believed the amplitude of the T wave to depend on hemodynamic conditions, while the S-T level at increased heart rate first is elevated and then becomes depressed, a finding that certainly has importance for all quantitative estimations of S-T depressions as in tolerance tests. Van Bogaert *et al.* studied experimental modifications of the process of repolarization in dogs (255) and in patients with arterial hypertension (256). Critical viewpoints with regard to the "improvement" of hypertensive electrocardiographic patterns were expressed by Palmer (257), while Boyer & Hewitt (258), who subjected the electrocardiogram before and immediately after sympathectomy for hypertension to vector analysis, expressed the opinion that both the alterations due to the hypertension and those secondary to successful surgical treatment were mainly dependent upon change of the position of the heart in the thorax. If this somewhat surprising explanation is confirmed, it may challenge the idea of electrocardiographic coronary insufficiency. The electrocardiographic diagnosis of cardiac aneurysm has been studied by several workers (259 to 264).

Rhythmicity and arrhythmias.—Studies on the nervous influence upon cardiac activity include: spike potentials and cardiac effects of mammalian vagus nerve activity (265), electrocardiographic effects of vagal tone (266, 267) and vagal stimulation in dogs with particular reference to R-R and P-R intervals and shape of the P-wave (268), the relationship between atrial and ventricular rate and the influence of autonomic factors upon this relationship (269), and the induction of conditioned reflexes influencing heart rate in human subjects (270). Chapman *et al.* (271) found that regulation of arterial pressure and heart rate in man involves the olfactory cortex and mesocortex. Chatfield & Lyman (272) studied the circulatory changes during the process of arousal in the hibernating hamster. The process of hibernation seems to be governed by heat control centers in the hypothalamus, and it may be of primary importance to investigate the precise cerebral mechanism by which cardiac metabolism and cardiac activity is controlled.

The influence of premature impulses upon cardiac pacemakers was studied by Pick *et al.* (273) with reference also to its bearing upon Stokes-Adams' syndrome. Retrograde conduction from premature ventricular contractions was investigated by Kistin & Landowne (274) by means of esophageal leads in 33 cases. The authors believe the concept of a normal unidirectional block in the atrioventricular node to be untenable. The influence of premature beats on the rheocardiogram and their hemodynamic effects was studied by Breu & Vetter (275). Hellerstein *et al.* (276) constructed an extracorporeal electronic by-pass of the atrioventricular node which was able to produce W-P-W³ syndromes and to institute normal synchronism between atria and ventricles in complete heart block. With the application of cardiac catheters, the apparatus should be of value in the treatment of acute complete heart block in man.

Also, the genuine W-P-W syndrome has attracted interest and has been

³ Wolff-Parkinson-White.

studied by means of intracardiac and esophageal leads by Grishman *et al.* (277) and by electrokymographic means by Samet *et al.* (278) and by Dack *et al.* (279). Asynchronism in ventricular ejection does not seem to be a typical feature of this syndrome. Earlier activation of subepicardial heart muscle than of subendocardial is advanced by Kisch (280) as a possible explanation of the syndrome.

Scherf *et al.* (281) continued their experiments with application of aconitine on the ventricular surface which induces ventricular fibrillation. Scherf & Chick (282) found acetylcholine topically administered to the atrial or ventricular surfaces of the dog's heart capable of inducing various arrhythmias. Atropine diminished the response but did not completely abolish it. The bearing of their findings upon the arrhythmias encountered by vagal stimulation in man was discussed. Direct leads from the human atria were found to support Scherf's view that polyfocal stimulation must be present in atrial flutter (283). Steinberg *et al.* (284) studied the electrical cycle in atrial flutter by means of atrial vectocardiograms from intracardiac, esophageal, and precordial leads. They maintained, however, that the vectors obtained proved the presence of circus movements and thus supported Sir Thomas Lewis's original conception. Söderström (285) considered the question of the cause of the ventricular arrhythmia in atrial fibrillation. By plotting R-R intervals on special charts he found that these intervals accumulated at time levels that were strikingly constant from one case to another. Besoain-Santander *et al.* (286) investigated the irregular ventricular response in some cases of atrial flutter and believed a mechanism similar to second degree atrioventricular block to play a role. Brandman *et al.* (287) reported five cases of atrial flutter with complete heart block.

Several papers deal with the trial of new drugs for prevention and treatment of arrhythmias, particularly such arrhythmias as are encountered during operations and cardiac catheterization. Procaine and procaine amide (pronestyl) have been tested by various workers. Favorable experiences with these drugs were reported by several authors (288 to 292), while others (293, 294, 295) were less impressed. The experience of the reviewer is in accordance with the former opinion. Frank *et al.* (296) in experimental studies on ventricular fibrillation in dogs demonstrated that procaine in all the doses tested slowed the rate of fibrillation, gave rise to weak, inefficient coordinated contractions with doses less than 50 mg per kg. body weight, and induced ventricular standstill in doses of 200 mg. per kg. or more. Neither did Stearns *et al.* (297) under similar conditions find any beneficial effect of procaine. They maintain that hypotension is a dangerous side-effect of this drug. The only dependable agent against ventricular fibrillation still seems to be electrical countershock.

Enselberg *et al.* (298) reported two cases of ventricular fibrillation after intravenous administration of acetyl strophanthidin, with fatal outcome in one. Mercurial diuretics (15 mg. per kg. in dogs) regularly resulted in ventricular fibrillation (299). British antilewisite seemed to offer full and magnesium sulfate some protection, while countershock was most effective in re-

storing a normal rhythm. Further studies on the influence of mercury on the heart were presented by Farah *et al.* (300). Successful use of atropine sulfate in controlling ventricular tachycardia was reported by Bruce *et al.* (301), and its use in myocardial infarction in elderly people was advocated by Nalefski & Brown (302).

While Mosey & Stutzman (303) claimed that cyclopropane and ether improved or abolished arrhythmias produced in dogs by digitalis, Johnstone (304, 305) showed that cardiac inhibition to the point of complete arrest might be induced by these agents. Atropine was effective in preventing this standstill, but may instead cause ventricular tachycardia, particularly if the carbon dioxide tension is high. Inhibition of the excitability and contractility of isolated atria by anesthetics was also reported by Acierno & DiPalma (306).

Influence of humoral factors.—Much interest has been shown in the influence of electrolytes, particularly potassium, upon the electrocardiogram. Feigen *et al.* (307) studied the influence of ions, drugs, and temperature on the static condition and dynamic response of the surviving rat ventricle strip and Garb (308) the effect of five cations on the electrogram and myogram of mammalian papillary muscle. Green & Giarman (309) investigated the influence of potassium and calcium on mammalian myocardial activity within the physiological range and found excitability to be influenced by potassium but not contractility. Bellet *et al.* (310, 311) studied the effect of different concentrations of potassium on the electrocardiogram of normal dogs and dogs with myocardial infarction. The latter dogs were more sensitive to potassium than the normal ones. There was no correlation between the quantity of potassium administered and the terminal serum level of potassium. In normal dogs the effect on the electrocardiogram was reversible up to the stage of a marked degree of bundle branch block and ventricular tachycardia. Campbell & Friedman (312) found that potassium impaired but desoxycorticosterone acetate improved the electrocardiogram in acute heart injury in rats. The electrocardiogram of hypokalemic chickens was studied by Sturkie (313), who found diethylaminoethanol superior in restoring it to normal. Somerville *et al.* (314) studied electrocardiograms from 90 patients with Addison's disease. Abnormal tracings were found in 52 per cent. Desoxycorticosterone acetate did not produce any change in the electrocardiogram, while cortisone apparently did (315). The authors conclude that there is no specific electrocardiographic pattern of Addison's disease. The changes observed probably derived from many different sources. They also described disturbances of the cardiac mechanism in potassium intoxication (316). Currens *et al.* (317) presented indirect evidence that the electrocardiogram might be a better guide to intracellular potassium content than are serum levels. Myers (318) discussed alterations in serum potassium as a source of error in the electrocardiographic diagnosis of myocardial infarction, and Schlachman & Rosenberg (319) found that potassium salts were capable of causing an upright T in cases of T waves inverted from organic causes. Söderström (320) described the electrocardiogram in hyperkalemia in con-

nection with a low sodium diet. Other studies in this field include: influence of carotid chemoreceptors upon cardiac activity in hypoxia (321) and effects of carbon dioxide tension (322) and of thyroxine (323). Electrocardiographic changes associated with allergic reactions to penicillin were reported by Binder *et al.* (324).

HEMODYNAMICS; CARDIAC OUTPUT

Heart size and cavity capacity.—Hamilton *et al.* (325) discussed factors determining heart size in the intact animal and regarded heart rate as the most important single factor. Nylin (326), by means of P^{32} , continued his studies on the changes in the amount of residual blood of the heart in man. He believed a small amount of residual blood to exist even in normal conditions. Friedman (327) studied heart volume, myocardial volume, and total capacity of the heart cavities in certain chronic heart diseases and found, *inter alia*, surprisingly good correlation between post-mortem heart volume, determined roentgenologically according to Kahlstorf, and actual heart volume (measured by displacement). No attempt was made by either Friedman or Nylin to investigate the different cavities separately. Such studies, however, are greatly needed. *In vivo* determinations of residual blood volume in the right ventricle were reported by Heimbecker *et al.* (328). Residual blood in the normal right ventricle was calculated to be 60 cc. The presence of residual blood at the end of systole in both ventricles was further recorded in angiocardiograms by Rushmer *et al.* (329). Velazquez (330) also studied the capacity of heart cavities and found the greatest enlargement in valvular regurgitation and least enlargement in renal hypertension.

Influence of general dynamic factors.—Factors affecting cardiac output in man were reviewed by Cournand (331). Horwitz (332) considered the normal curve of cardiac ejection velocity to be consistent with the assumption that the individual cardiac muscle units shorten with a constant velocity. The duration of ventricular diastole was discussed by Groedel & Miller (333), and Remington (334) investigated the relation between the length of diastole and stroke index in the intact dog.

Gregersen & Nickerson (335) discussed the influence of body type upon normal values for blood volume and cardiac output. Taylor *et al.* (336) found that the blood flow through the fat was not important in determining cardiac output in obese subjects. The influence of peripheral circulatory factors was discussed by Guyton & Harris (337) and by Sjöstrand (338) and Johnsson (339), who believed that the blood depot function of the lungs might be of great importance in the regulation of cardiac output. The concepts of these authors were corroborated by studies made by Lagerlöf *et al.* (465) on circulatory changes after tilting to the upright position. Also pertinent to this discussion are papers by Hickam & Pryor (340) on cardiac output in postural hypotension and by Eddleman *et al.* (341) on the effects of vertical position on cardiac hemodynamics as recorded by the electrokymograph. Dexter *et al.* (342) reinvestigated the effects of exercise on circulatory dynamics in normal subjects and found increased cardiac output and arteriovenous

oxygen difference and no significant change of pulmonary arteriolar resistance.

Influence of humoral and nervous factors.—Investigations concerning the influence of certain metabolic conditions upon total cardiac output and blood flow through certain organs were carried out: by Bucht (343) regarding renal circulation in pregnancy, by Scheinberg *et al.* (344) on cerebral blood flow in myxedema, and by Myers *et al.* (345) on hepatic circulation in hyperthyroidism. An interesting study on the influence of autonomic reflexes, presumably mediated by vagus fibers, on the ventricular contractility that may help to explain difficulties in the application of Starling's law on man was presented by Peterson (346). Dickinson (347) found a linear relation between venous pressure and the frequency of electric discharge in afferent nerve fibers from the right atrium.

Pulmonary circulation.—Catheterization of the right heart has continued to direct the interest of many laboratories to studies on pulmonary circulation. This has been no less important since operation for mitral valvular disease has shown itself to be a practical procedure (*vide infra*). Courmand and co-workers (348, 349) have prepared comprehensive reviews of present knowledge of pulmonary circulation in normal man and in chronic cardiopulmonary disease. Recent studies in this field include: a monograph on chronic cor pulmonale (350), a presentation of chronic obstruction of major pulmonary arteries (351), interesting findings in a woman with selective pulmonary venous stasis (352), the effect of pericardial tamponade in the production of pulmonary congestion (353), and a method for producing controlled obstruction of pulmonary vessels and for studying the anatomical end results of this procedure (354).

A pulmonary artery pressor response to hypoxia and hypercapnia during perfusion of pulmonary vessels in isolated cat lungs was found by Duke (355) who, interestingly enough, suggests that this finding may be due to metabolic changes in the smooth muscles of the pulmonary vessels and not, as generally believed, to neurohumoral reflexes. This concept is in accordance with other recent trends toward investigation of cellular metabolism in the walls of the vascular tree (356, 357). Doyle *et al.* (358) studying the effects of breathing air with low oxygen content in normal men found an increase in pulmonary artery pressure with no change in pulmonary capillary pressure, while systemic vascular resistance tended to fall. Burchell & Wood (359) in three cases of patent ductus arteriosus found low oxygen breathing to cause a partial reversal of flow within the ductus, likewise indicating different effects upon pulmonary and systemic arterial pressure. Definite reversal of flow due to elevated pulmonary artery pressure in combined lesions in three cases was reported by Pritchard *et al.* (360).

Cardiac asthma and pulmonary edema were discussed by Sonne & Hilden (361) who found that high arterial pressure during the attack was associated with a more favorable prognosis. Visscher (362) reported that in experiments with dogs pulmonary edema did not occur unless pulmonary venous pressure was elevated. No evidence of direct effects of nervous factors upon pul-

monary capillary permeability was found. The influence of hypoxia in the genesis of pulmonary edema was attributed to left ventricular failure. Hemingway (363), however, was unable to produce pulmonary edema by means of induction of hypoxia. MacKay (364) and Patton & Gamble (365) as well as Sarnoff (366) were able, however, to demonstrate pulmonary edema of cerebral origin in rats and rabbits. Luisada (367) found that inhalation of ethyl alcohol, due to its antifoaming properties and its action on the central nervous system, was useful in the treatment of paroxysmal pulmonary edema.

Doyle *et al.* (368) found that rapid intravenous infusion of physiologic saline solutions in normal subjects induced significant increases in pulmonary artery and pulmonary capillary pressures. Dotter & Lukas (369) produced acute cor pulmonale in dogs by means of a special cardiac catheter with a rubber balloon and found right ventricular end diastolic pressure to be represented by a curve similar to that of Starling's law. Right axis deviation did not appear in the electrocardiogram, which is in accord with the concept that axis deviation is an expression of positional change or change in functioning ventricular muscle mass. Daley *et al.* (370) injected lycopodium spores into the pulmonary artery of dogs and found extensive interference with autonomic nervous influence not to affect the induced pulmonary hypertension. Fowler *et al.* (371), however, found tetraethylammonium chloride to affect elevated pulmonary arteriolar pressures in man and claimed that autonomic nervous tone participates in pulmonary hypertension. Though everyone who has studied pressures in the pulmonary circulation may at some times be in doubt whether or not such influences may invalidate his experiments, there also are, as in these authors' studies on norepinephrine (372) where no pulmonary effects were encountered and in those of Werkö *et al.* (373) and of Steinberg *et al.* (374) on theophylline, factors related to cardiac output to take into consideration. It is quite obvious that further investigations into this fundamental point are necessary, but little satisfactory evidence in favor of a direct autonomic influence has as yet been presented.

Congenital heart disease.—Of the vast number of papers on this subject some may be mentioned, viz., those concerned with the dynamics of coarctation of the aorta (375, 376), of isolated pulmonary stenosis (377), and of *grosses pulmonaires* (large pulmonary arteries) (378); a technique for the experimental production of pulmonary artery stenosis (379) and promising results of surgical therapy in pulmonary stenosis (380, 381, 382); the results of 412 operated cases of patent ductus arteriosus (383); and the relation between the Eisenmenger complex and uncomplicated ventricular septal defect (384). Barber *et al.* (385) reviewed 62 cases of atrial septal defect and claimed absence of pulmonary hypertension to be a constant and noteworthy finding. Nahas *et al.* (386) in such cases found a pressure gradient between the pulmonary veins and the right atrium which they attributed to pressure transmitted by the right ventricle and which they believe to operate in the atrial shunt mechanism. In connection with studies on the effect of normal and abnormal respiration on the hemodynamics of experimental atrial septal de-

fects (387, 388), Opdyke & Brecher also studied the effect of experimental atrial septal defects in dogs rendered "mitral stenotic" (389). The additional defect seemed to exert little influence, and no relief of left atrial pressure was observed in the acute experiment, the nature of which, however, does not permit drawing any conclusions for clinical medicine. Various other cardiac shunts were produced and studied by Katz *et al.* (390).

The intriguing problems of the pulmonary and cellular respiratory adjustments in cyanotic congenital heart disease have been studied by Ernsting & Shephard (391), who believe the sigmoid shape of the normal oxygen dissociation curve of hemoglobin to account for the ease with which adaptation to low oxygen tension is achieved. Slight displacement of the dissociation curve to the right in such patients was reported by Morse *et al.* (392). Prader *et al.* (393, 394, 395) studied iron and hemoglobin metabolism in such cases as well as characteristics of blood corpuscular elements in cyanotic heart disease. Havel & Watkins (396) found normal lactate and pyruvate concentrations of cubital vein blood in children with cyanotic heart disease but a delayed return to normal levels after exercise. The significance of such observations is debatable. The structure of clubbed fingers was further studied by Lovell (397).

Mitral valvular disease.—The last decade has witnessed the remarkable progress in the surgical correction of congenital heart disease by operations on the large vessels in the immediate vicinity of the heart. These congenital lesions, though more frequent than previously recognized, are, however, rare in comparison with acquired valvular heart disease. Apart from single daring experiments, few attempts have, until recently, been made in the field of intracardiac surgery. This hesitation may be partly explained by the inclination to await the perfection of an "artificial heart," permitting more direct approaches to the interior of the heart to be operated upon. As yet, however, no serious reports on successful use of artificial hearts or other arrangements [such as the isolated homologous lung as donor oxygenator (398)] in patients have been published.

In spite of this, intracardiac surgery has proved possible without undue risks, and during the period to be covered a great number of reports on successful surgical treatment of various valvular lesions have appeared, chiefly dealing with the most frequent and most easily accessible defect, mitral stenosis (399, 400, 401), but also with mitral insufficiency (402, 403), aortic stenosis (404), and pulmonary stenosis (380, 381, 382). While the procedures in mitral insufficiency and aortic stenosis still seem to dwell on an experimental stage, in the opinion of the reviewer valvulotomy or comparable surgical dilatation in mitral stenosis, despite the scepticism expressed by Wilcox & Grace (405), has definitely come to stay and will present a quantitative problem.

While it is true, that only a far-reaching follow-up study can definitely evaluate the results and determine the proper indications for these operations, it is already clear, that the methods of clinically applied physiology have a decisive place in the immediate study of these patients. They will

supplement other procedures in establishing the clinical diagnosis and are indispensable in the analysis of such factors as: the area of the valvular orifice, the relative degrees of stenosis and regurgitation, and the presence of primary myocardial weakness (left and right) and secondary pulmonary vascular changes, which must determine the selection of cases for operation and aid correspondingly in the postoperative evaluation of the results.

Several groups have already reported their studies on circulatory dynamics in mitral valvular disease. Particular interest has been aroused in the prediction of the orificial area by Gorlin *et al.* (406 to 409) who presented a hydraulic formula for its calculation. Also pertinent to the theoretical discussion of this point is a paper on resistance in valve models by Müller (410). While some workers believe it possible to differentiate between mitral stenosis and mitral insufficiency by means of so-called pulmonary capillary pressure tracings, Draper *et al.* (411) believed a differentiation difficult, though possible. They maintained that patients with mitral insufficiency generally had a lower resting cardiac output, a higher arteriovenous oxygen difference, and a greater fall in cardiac output with exercise than in patients with (predominant) mitral stenosis. The effect of exercise on pulmonary vascular pressures and on cardiac output were further studied by Dexter *et al.* (342, 412, 413) and by Campbell & Selverstone (414). Pulmonary artery and capillary pressures rose, while pulmonary vascular resistance showed little change, and sometimes fell (413). Cardiac output did not increase in anything like the normal way and might even fall, while right ventricular work was greatly increased. One of the important problems in the study of the exercise tolerance of candidates for operation is to choose a type of exercise that can be maintained a sufficiently long time to permit a steady state without at the same time causing undue fatigue and perhaps induce pulmonary edema.

The role of electrokymography in determining the degree of mitral insufficiency in mitral stenosis is still difficult to evaluate. Though Froment *et al.* (415) arrived at essentially negative conclusions concerning the interpretation of left atrial expansion as a sign of mitral insufficiency, the reviewer feels that it may yield useful information in cases with regular heart action.

The degree of myocardial damage of the right ventricle may, as mentioned, be studied by catheterization, but the question of the possible damage of the left ventricle is harder to evaluate, though of great significance in the prediction of its power to adapt itself to a suddenly increased blood flow. Some indications may be had from the electrocardiogram, though the presence of digitalis sometimes interferes with its interpretation. Further studies are needed here.

As already indicated by Borden *et al.* (416), pulmonary hypertension is not entirely due to elevation at left atrial pressure but in part also to an increased vascular resistance in the lungs. Draper *et al.* (411) pointed out that this vascular resistance may not be fixed, as it can decrease in exercise and after valvulotomy, but Welch *et al.* (417) stressed that such changes may be so great and so fixed as to be the very bottle-neck of the lesser circulation; such patients are not likely to benefit from valvulotomy. A lucid discussion

of the interrelationship between pulmonary capillary pressures and the blood flow through the mitral orifice was presented by Gorlin *et al.* (418). Becker *et al.* (419) found the same type of occlusive pulmonary vascular changes in mitral insufficiency as in mitral stenosis. Munnell & Lam (420) believed it possible to predict the degree of therapeutic success by direct studies of the left atrial and pulmonary artery pressures in connection with the operative procedure.

Another important problem is the prediction of atrial thrombi and the estimation of the size of the auricular appendage. From personal experience the reviewer feels that angiocardiology also has a definite place in the evaluation of mitral valvular disease. Jordan *et al.* (421) investigated 51 cases of mitral stenosis with mural thrombi and found half of those in the left atrium restricted to the appendage. Resection of auricular appendages has been proposed as a method for the prevention of peripheral emboli in rheumatic heart disease with auricular fibrillation and embolic phenomena by Beal *et al.* (422).

Only a sufficiently large critically evaluated collection of all available data—clinical, physiological, and roentgenographic—on candidates for operation will permit a final decision as to which signs and methods prove most reliable.

Arteriovenous fistulas.—Small arteriovenous communications of considerably greater caliber than capillaries were found in human lungs without pulmonary pathology by Tobin & Zariquiey (423). The effect of arteriovenous fistulas in the greater circulation upon cardiac output (424) and blood volume (425) and the changes induced by their temporary occlusion (426) were investigated by Warren *et al.*

Miscellaneous.—Laszt & Müller (427) described pressure curves from left atrium, ventricle, and aorta ascendens in dogs. Left ventricular pressures in compensated and decompensated aortic valvular lesions were studied by Zimmerman (428); a definitely increased diastolic pressure was found in the latter group. Acute atrial fibrillation induced experimentally in dogs by Wégria *et al.* (429) produced little change in cardiac output, coronary blood flow, or mean arterial pressure except for the first few seconds after its induction. Interesting variations in the cardiovascular response to stress among hypertensive patients as studied by the ballistocardiograph were revealed by Flynn & Wolf (430) who found two types, one with lowered, the other with elevated peripheral resistance.

CARDIAC FAILURE

While dynamic factors in the genesis of heart muscle failure have been thoroughly studied, the metabolic aspects until now have been less well investigated. The majority of the papers of the year within this section deal with volume and composition of plasma and extracellular fluid in cardiac failure and with the renal mechanisms involved. The extent to which electrolyte disturbances are due to failure or to independent factors was discussed by Proger & O'Connor (431). Weston *et al.* (432, 433) attempted an evaluation of the influence of hormonal and nutritional influences in congestive

failure. Galeone *et al.* (434) found low coenzyme blood values in congestive failure which they regarded as an effect of tissue hypoxia. Digitalization was followed by a rise in coenzyme content. A tendency to low serum protein in failure again was reported by Niggli (435). Aikawa *et al.* (436) found that 1.2 mg. digitoxin intravenously in five normal men caused an increase in the water and protein content of the vascular compartment. Felder *et al.* (437) found definite impairment of liver function in congestive failure but no specific pattern of liver function test disturbance could be identified. The administration of 50 gm. of serum albumin intravenously daily for a week was found by Gimbel *et al.* (438) to induce congestive heart failure in healthy young males. According to Bercu *et al.* (439), a concentrated dialysate of urine from most of their patients with cardiac failure injected into dogs had an antidiuretic action. This action should not be attributable to pitressin. Differences in diurnal patterns of renal function in congestive heart failure and in normal subjects were revealed by Baldwin *et al.* (440). Grossman *et al.* (441) found in cardiac failure a normal maximal tubular capacity for the excretion of *p*-aminohippurate and the reabsorption of glucose, but low glomerular filtration rates and renal plasma flow. Surtshin *et al.* (442), studying hypophysectomized dogs with subsequently lowered renal blood flow and filtration rate, found no evidence of sodium retention and therefore doubted that reduced glomerular filtration rate per se was the causative factor of tubular sodium retention. The effects of human myocardial infarction upon plasma electrolytes and 17-ketosteroids were studied by Sampson *et al.* (443) and also the relationship to eosinophile counts, by Forssman (444).

The effects of low-sodium and even Kempner's rice diet in congestive failure and in hypertensive heart disease continued to be studied by various workers. Thus, Murphy (445) found a marked decrease in plasma volume, blood volume, and extracellular fluid after 14 weeks of rice diet. Clinical symptoms of sodium depletion appeared early in the course but not at the end of the treatment. Careful observations as to the movements of water, sodium, and potassium during recovery from congestive failure on a 50 mg. sodium diet were presented by Iseri *et al.* (446), indicating cellular release of water and uptake of sodium and potassium with coincident osmotic inactivation of cell base. Watkin *et al.* (447, 448) also made very thorough studies on the effect of rice diet in essential hypertension, which corroborate Kempner's statements. Like Starke (449), they also considered the effect of rice diet on cholesterol metabolism and, in agreement with Corcoran *et al.* (450), they believed that the rice diet essentially is a low-sodium diet, the protein restriction of which probably has been unnecessarily rigid. Dole *et al.* (451) believed the success of the Kempner diet to be due less to a depletion of sodium than to a successful adaptation to a new steady state of limited sodium supply.

Walton *et al.* (452) investigated the comparative increase in ventricular contractile force induced by various digitalis glycosides. In a few instances maximal contractile force changes preceded by a distinct interval any significant change in the electrocardiogram. The influence of the magnesium

ion on the heart and its response to digoxin was studied by Stanbury & Farah (453). Lown *et al.* (454) found potassium deficiency to increase the sensitivity to cardiac glycosides. According to Sciarini & Salter (455), chemical (fluorescence) determination of digitalis potency correlated reasonably well with oral potency in man but less so with biological assays in cats and pigeons. The low prediction value of frog heart assays for digitalis was emphasized by Walton *et al.* (456). Siedek & Tomek (457) claimed that each type of cardiac lesion has its digitalis preparation of choice. Pardo *et al.* (458, 459) studied the effect of several principles of the digitalis group upon ischemic skeletal muscle and found a marked increase in the amplitude of contraction.

The distribution of mercurial diuretics in some of the body fluids was investigated by means of radiomercury by Ray *et al.* (460). Low concentrations were found in edema and transudates, high concentration in the bile. Edlund & Linderholm (461) believed the effect of mercurial diuretics in mobilizing fluid to be due at least partly to a spreading factor effect. The increased use of mercurial diuretics by the more uncontrolled subcutaneous route forced Jaffe *et al.* (462) to draw attention to the hazards of the salt depletion syndrome and also to symptoms of prostatism.

Two recent attempts to summarize present views on congestive heart failure should be mentioned, viz., the article by Burch & Ray (463) and the book by Youmans & Huckins (464).

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THE LYMPHATIC SYSTEM

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The literature dealt with in this paper is by no means all-inclusive for the period since 1949. Only those articles dealing directly with lymphatic vessels or lymph nodes are reviewed. No attempt has been made to catalogue all references to lymph nodes mentioned in clinical literature. That some subjects are discussed in more detail than others reflects only the interest of the writer and does not mean necessarily that other material is considered relatively unimportant.

LYMPHATICS

Drainage from peritoneal cavity.—Investigations of pleural and peritoneal drainage have been confined to two chief categories; pathways of absorption of inert particles and absorption of fluids. Studies reveal that the maximum diameter of a particle passing through the peritoneal mesothelium of the diaphragm after its injection into the peritoneal cavity of the rat is 5 to 6 μ [Simer (1)]. The material from there on is carried through the sternal lymph trunks into the mediastinal nodes or through lymphatics in the diaphragmatic crura to the lumbar nodes. Such observations resurrect the old question of the presence of diaphragmatic stomata [Allen (2)]. An answer to this is that small particles pass freely into the subperitoneal lymphatics, appearing to force their way between the contiguous borders of the diaphragmatic mesothelial cells and the endothelial cells of the lymphatics.

When dye, T1824, combined with plasma protein is introduced into the peritoneal cavity of the cat and rabbit, much of it is absorbed by the diaphragmatic lymphatics; it then passes into the blood stream mainly through the right lymph duct during the first 2 hr. [Courtice & Steinbeck (3)]. This indicates that the dye protein passes rapidly into the diaphragmatic lymphatics and then by the parasternal vessels mainly to the right lymph duct, while passage through the omentum, mesentery, and parietal peritoneum into the thoracic duct is slower, a ratio of four to one over a 5-hour period.

Drainage from pleural cavity.—The right lymph duct also plays a major role in the lymphatic drainage of the pleural cavity [Courtice & Simmonds (4)]. Anesthesia slows down pleural absorption in the rabbit and cat. Both 0.9 per cent sodium chloride and plasma are absorbed at the same rate in the unanesthetized animals. Compared with absorption from the pleural cavities, absorption of plasma from the peritoneal cavity is rapid [Courtice & Steinbeck (5)]. The rate in the rabbit is definitely more rapid than in the guinea pig. A contradiction results from the comparison of the absorption rates of 0.9 per cent sodium chloride and plasma from the peritoneal cavities

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in guinea pigs and rabbits. Absorption of plasma is much greater than saline in the rabbit, but the two are absorbed at the same rate and more slowly in the guinea pig.

Drainage from lungs.—Dye-protein is absorbed from the lungs of rabbits at a much slower rate than is sodium chloride [Courtice & Simmonds (6)]. The removal of protein-rich fluids is more rapidly effected from the pleural cavities. Some of these experiments indicate that lymph collected from the lung and pleural cavities does not pass entirely into the blood stream via the right lymph duct. A portion, especially in animals other than the dog, is collected by the thoracic duct. Throughout the discussions of the above investigators, the statement appears that protein absorption from these areas occurs by means of lymphatics, whereas dye, T1824, dissolved in distilled water is absorbed directly into the blood stream. An examination of diaphragms and mediastina of guinea pigs after intraperitoneal injection revealed the contents of lymphatics to be either dye-stained plasma or dye dissolved in saline [Courtice (7)].

Thoracic and right lymphatic ducts.—Increased lymph flow from the right lymphatic duct is correlated with the onset and progression of pulmonary edema produced experimentally in dogs [Paine *et al.* (8)]. Collection of lymph from this region is facilitated by making a simple incision, controlling bleeding, and sponging up the lymph from the incised vessels on weighed cotton pledgets [Paine *et al.* (9)]. Flow can be determined quite accurately if they are weighed again at once after the collection.

An easy but adequate method of demonstrating the thoracic duct roentgenographically in cadaver and postmortem material can be employed to show the wide variations of this structure in the human [Lowman *et al.* (10)]. Accidental ligation of the thoracic duct in humans is not accompanied by subjective complaints [Ehrenhaft *et al.* (11)]. Blood-fat level is reduced sharply to half but climbs to normal within two weeks. This is not surprising in that the establishment of new circuits for lymph flow occurs within that period [Simer & Webb (12)]. A comparison of the effects of ligation and those of excising the thoracic duct in the dog demonstrates the relative mildness of symptoms following ligation in contrast to the severe symptoms following excision [Hodge & Bridges (13)].

Propulsion of lymph.—The forces resulting in the propulsion of lymph remain clouded even today. At the present time little can be added to the conclusion of Sheldon (14) that muscular power of the vessel, assisted by the collateral pressure produced by respiration and by adjacent muscles and arteries, will impel the fluid towards the heart. It is true that not all investigations result in the expression of all the possibilities mentioned above. As a result, the explanation of the causes of movement of lymph can be divided into two categories, one based on intrinsic mechanism and the other on extrinsic factors.

Perusing the literature dealing with extrinsic factors, one encounters statements based on direct or indirect observations. The rate of pleural ab-

sorption is greatly increased with lung movement [Courtice & Simmonds (4)]. The effect of respiratory movements, when stimulated by carbon dioxide, on the absorption from the peritoneal cavity of the cat is considerable [Courtice & Steinbeck (3)]. Plasma rapidly enters the diaphragm and is forced along lymphatic channels by respiratory movements.

Once protein enters the mediastinal lymphatics, the same forces, those due to respiratory movement, are responsible for the propulsion of lymph through lymph channels ultimately to the blood stream [Courtice & Steinbeck (5)]. These authors used guinea pigs and rabbits in their experiments and found that somewhat divergent behavior between the lymphatics of the two animals occurred. Mammalian lymph flows normally by muscle contraction, massage, active and passive motion of the body, gravity, tissue pressure, and pulsation transmitted from arteries to lymph vessels [Robison (15)]. One possibility is omitted from this statement; the intrinsic mechanism within the walls of the lymphatic involved.

Ottaviani (16) straddles the issue in his implication that visceral lymphatics are passive in the impelling mechanism, whereas the peripheral lymphatics participate in the production of active forces. In his study of the bat, in which he observed exquisite contractible capacity in the wing, he was forced to state that the whole mesenteric vessel system possesses a life of its own.

The most peripheral lymphatic vessels of rats, mice, and guinea pigs possess a spontaneous intermittent contractility [Smith (17)]. This verifies observations on the bat which were ignored by the previous writer [Webb & Nicoll (18)]. Such contractions appear in the walls of all types of lymphatics of the bat and are especially vigorous in the most peripheral capillaries which in reality are enormous bulbular enlargements. Changes in rate of contraction and in caliber of vessels in the rat and guinea pig result from the topical application of epinephrine and pituitrin [Smith (17)]. This again verified the results of topical application of drugs to the mesenteric lymphatics of the rat [Webb (19)]. Similar studies on the dog and rabbit revealed that the drugs affect the caliber of their lymphatics but obviously not the rhythm because such spontaneous contractions do not appear in the lymphatics of these animals.

Sectioning of the nerves supplying areas of the bat's wing gives evidence that the lymphatics are not dependent on neural control [Webb & Nicoll (20)]. The rhythmic pulsations continue despite their separation from central nervous system control. Using the dog as an experimental animal, Rusznyák *et al.* (21) find that faradic stimulation of the lumbar section of the sympathetic chain results in spastic constriction of the lymphatic vessels.

In summarizing the data on animals which have been studied from the viewpoint of determining whether or not rhythmic contractions of lymphatics contribute to the forces which propel lymph, the following grouping can be made. Definite spontaneous contractions have been observed in the bat, rat, and guinea pig. No spontaneous contractions have been demon-

strated in the cat, dog, rabbit, and squirrel. Similar mechanisms in lymphatics of mice are a subject of debate. The few casual observations in man have shown none.

An explanation of the forces producing rhythmical contractions in blood vessels and lymphatics is illustrated by experiments on a hydrostatic model [Young & Griffith (22)]. Proceeding on the thesis that all living tissues exemplify a differential pressure system with a wide range of variability, a hydrostatic model was set up to elucidate a few of the characteristics of a simple differential system. The model consists of a perplex box, transparent tubing, and three manometers for measuring proximal and distal internal pressures and external pressure of the surrounding medium. The two systems then were connected to tanks whose heights regulated the pressures. Oscillation of the tube, representing the lymphatic or blood vessel, is a function of the differential pressure and is not conditioned by absolute values of internal and external pressures. It can be maintained indefinitely by adjusting the differential pressure so that the external pressure lies at any point between that indicated by the proximal and distal manometers.

Excessive pressure, producing distention of the lymphatics, can reach the point where the valves are no longer competent to prevent retrograde flow. This occurs in cases of elephantiasis in the human [Servelle & Deysson (23)] and is demonstrated by injection of opaque substances. In the normal subject, lymph flows centrally toward the collecting node.

Rate of lymph flow.—Average rate of flow of hepatic lymph in the dog is 2.25 cc. per 10 min. as compared with 4.6 cc. for that of lymph in the thoracic duct [Cain *et al.* (24)]. Intravenous administration of a 20 per cent solution of glucose is followed by an increase of 70 per cent in the rate of flow from both liver and thoracic duct. Ingestion of food increases flow from the thoracic duct 80 per cent and that of hepatic lymph 105 per cent. A similar technique for collection of lymph from the liver, small intestine, or thoracic duct of the rat has made possible a wide variety of studies on the chemical constituents of lymph and the possibility of their alteration by feeding experiments [Bollman *et al.* (25)]. In normal rats, the following quantities of lymph can be collected in 24 hr.: liver 5 cc., intestine 20 cc., and thoracic duct 25 cc. The ingestion of 1 per cent sodium chloride solution by the fed animal causes an increase in rate of lymph flow which is out of proportion to that seen in control animals [Reinhardt & Bloom (26)]. Direct measurement of intestinal lymph flow following simple obstruction of the ileum in the rat proves that the rate of flow continues to be normal [Balfour *et al.* (27)].

Ether anesthesia in comparison with sodium pentobarbital has no significant effect on lymph flow in the cat, which is contrary to their effect on the dog [Flinker & McCarrel (28)]. A possible explanation of these differences may be offered by Hungerford & Reinhardt (29). Lymph flow in young (40-day) rats is labile in response to ether or sodium pentobarbital anesthesia in comparison with older (60 to 100-day) rats in which the rates of flow are not altered significantly. Thus, ether anesthetization in the young rat pro-

duces 30 per cent increase in flow from the lymphatic fistula as compared with the flow under sodium pentobarbital anesthesia. These differences are not noted in the older groups. When the effects of cyclopropane and ether on lymph production are compared under standardized conditions in dogs, cyclopropane is found to cause production of less lymph than ether, regardless of which agent is administered first [Beecher *et al.* (30)]. Lymph flow in the dog and cat increases during oxygen want as well as during increased expiratory resistance [Beznák & Liljestrand (31)].

Lymph flow from the skin of dogs contaminated with mustard gas increases, and the protein concentration approaches that of the plasma [Cameron & Courtice (32)]. Lymph collected from vessels draining the contaminated area inhibits the growth of bone-marrow fragments in tissue culture, indicating the presence of mustard gas or a toxic derivative.

Absorption by lymphatics.—A marked increase in activity of alkaline phosphatase of the intestinal lymph following feeding occurs in the rat [Flock & Bollman (33)]. This is abolished or greatly diminished in rats with ligation of the bile duct or biliary fistula [Flock & Bollman (34)]. Thus, it appears that bile in the intestine is somehow involved in the transport or release of alkaline phosphatase from the intestinal mucosa as well as in the absorption of fat. An increase in tributyrinase secreted after the feeding of a fat-containing meal is much greater than can be accounted for by the increase in lymph volume. A similar increase in alkaline phosphatase appears to represent a specific effect of ingested fat on the chemical composition of the intestinal lymph [Flock & Bollman (35)]. This parallel activity does not occur with amylase, nor is the intestine (via the intestinal lymph) a major factor in the formation of plasma protein [Bollman & Flock (36)]. However, more than half of the total circulating plasma proteins pass through the thoracic duct daily [Nix *et al.* (37)].

Since the concentration of phospholipid but not of cholesterol increases in the intestinal lymph during absorption of fat, it is probable that the mucosa of the small intestine is a source of plasma phospholipids as well as neutral fat via the lymphatic system during the absorption of fat [Bollman *et al.* (38)]. The concentration of cholesterol in intestinal lymph of the rat increases after a fatty meal, and much higher concentrations are found when cholesterol is fed in the diet [Bollman & Flock (39)]. The fat-soluble vitamin K appears to be absorbed exclusively through the lymph [Mann & Higgins (40)].

The possibility of the existence of accessory lymphaticovenous connections should be considered when studies are carried out on lymph obtained from the cannulated thoracic duct of the dog [Glenn *et al.* (41)]. Loss of protein through such a fistula in the presence of a protein-free diet, in the course of a few days, will markedly reduce the serum-protein concentration.

Observations on this type of fistula (chylothorax) in a patient indicate that when a meal containing stained neutral fat was given, a substantial amount of the dye was recovered from the chylothorax, whereas, when the

equivalent amounts of stained fatty acid and glycerol were given, little or no dye was recovered [Auld & Needham (42)]. These observations tend to give credence to the statement that fatty acids after ingestion go to the liver via the portal blood stream and that unhydrolyzed glycerides go via the lymphatics eventually to reach the fat depots [Frazer (43)].

A considerable amount of evidence is accumulating to cast doubt as to the accuracy of Frazer's statement. The higher content of conjugated acid in the fat depots after glyceride feeding is matched by its higher content in the liver and pooled organs [Reiser (44)]. In whatever form fed, free fatty acids are absorbed by the same route as are triglycerides [Reiser & Bryson (45)]. Unanesthetized rats, into whose thoracic ducts or lacteals cannulae had been introduced, were fed C^{14} -labeled palmitic acid either as triglyceride or the free acid. From 70 to 92 per cent of the absorbed labeled fatty acid was recovered as fatty acid C^{14} from the thoracic duct and 69 to 84 per cent from the intestinal lymph [Bloom *et al.* (46)]. A further study testing the participation of lymph phospholipids in carrying absorbed fatty acids from the small intestine to the plasma revealed that the amounts of recovered fats could be as much as 96 per cent [Bloom *et al.* (47)]. Transport of long-chain fatty acids, regardless of whether they consist of an even or odd number of carbons, is a concern almost exclusive of lymph [Chaikoff *et al.* (48)].

Ferritin is involved in the phenomenon of iron absorption through the intestine of the horse. The lymphatic system is concerned with iron absorption since the protein increases markedly in the mesenteric lymph nodes as well as in the intestinal mucosa after feeding ferrous ammonium sulfate containing 30 gm. of iron [Gabrio & Salomon (49)]. Apparently iron-protein linkage is present in lymph. The iron content of intestinal lymph of rats maintained on a normal diet is relatively constant in lymph collected from the intestinal lymphatics [Kolar & Mann (50)].

Histaminase content of lymph.—The lymph of the dog is very potent in destroying histamine. On the average this activity is 30 times greater than that of plasma [Carlsten *et al.* (51)]. This histaminolytic activity of lymph is not changed by reactive hyperemia [Carlsten *et al.* (52)]. A simple method for determining the histaminolytic activity of lymph or plasma suitable for estimating low values is described [Carlsten & Wood (53)]. The histaminase of the thoracic duct lymph originates chiefly from the kidneys and the gut [Carlsten (54)]. In pregnancy, the histaminase content of the thoracic duct lymph seems to be of the same order as in nonpregnant cats [Carlsten (55)]. Adrenalectomy is followed by a marked increase in histaminase content of this lymph which reaches a maximum within 2 hr. and persists approximately 24 hr. [Carlsten (56)]. Infusion of an adrenocortical extract will reverse this increased histaminase activity after adrenalectomy [Carlsten & Wood (57)].

Changes in lymph following irradiation.—Following 1,500 r whole body irradiation, the lymphocyte count per cubic millimeter and the total lymphocytes per unit of time in the thoracic duct lymph of cats rapidly become depressed when a comparison is made with determinations in normal animals

subjected to cannulation [Valentine *et al.* (58)]. When the lymph content of protein, uric acid, nonprotein nitrogen, creatinine, sugar, and chloride levels of control animals (dog) is compared with thoracic duct lymph of dogs exposed to 500 r total body x-radiation, the following changes occur [Brown *et al.* (59)]. Lymph total protein fluctuates at first, then decreases. Uric acid and nonprotein nitrogen increase the first 4 hr., then decrease slightly below normal. Lymph creatinine decreases, but after 18 hr. rises toward the normal level. The number of white blood cells drops precipitously. Marked capillary permeability is assayed in dogs and rats exposed to approximately LD₅₀ doses of x-ray by the appearance of large numbers of erythrocytes in the lymph collected from the thoracic duct [Bigelow *et al.* (60)].

Effect of extreme temperatures on lymph formation.—The threshold of burn trauma which registers as an increase in flow and protein concentration of the lymph draining from the burned foot of the dog is found to be an immersion time of 10 sec. in hot water of 67°C. [Cope *et al.* (61)]. Immersions at higher temperatures are followed by more precipitous and higher rises in lymph flow and protein concentration. Lymph flow from the burned foot is reduced sharply during a period of immersion in a cold (10°C.) bath, and the rise in protein concentration of the lymph and in rate of edema formation is also retarded [Langohr *et al.* (62)]. From the frostbitten foot of the dog, there is invariably an increase of lymph flow and protein concentration comparable to that following a burn; the onset of flow is delayed by freezing and greatly accelerated by thawing [Rosenfeld *et al.* (63)]. Experiments with restrictive dressings on burns show that they do not sufficiently reduce the increased lymph flow for the lymphatic vessels to be able to carry it [Rhinelander *et al.* (64)]. Unable to return to the blood stream, the lymph piles up as edema in the interstitial spaces proximal to the cast.

Recent anatomical studies.—Little attention has been paid to the distribution of the blood vessels and lymphatics of tendons, although an understanding of these channels is of great importance when one is considering their surgical treatment [Edwards (65)]. The tendon and the synovial sheath have one artery in the center, two venae comitantes, and lymphatics disposed as four main channels, one on each side of the veins. They are connected with one another along their whole extent by an intricate system of transverse vessels which surround the artery and veins. Both veins and lymphatics are devoid of valves in the visceral synovial membrane, but they do occur in the mesotendons or the loose folds of synovial membrane.

Contrary to the classical statement that the lymphatics of the spleen are limited to the superficial capsular plexus with branches sometimes entering the larger trabeculae, a deep lymphatic system is present in the spleens of guinea pigs as well as other mammals [Snook (66)]. In the guinea pig, mole, and mouse, they follow the course of the white pulp arteries to open into the lymphatic vessels at the hilus. In the horse, they can be traced into trabecular and capsular lymphatic plexuses.

Lymphatic channels are of cavernous proportions in the mucosal folds

of the ampulla and in the fimbriae of the Fallopian tube [Ramsey (67)]. When only moderately distended, the main bulk of the fimbriae is contributed by the lymphatics. The mucosal lymphatics are so capacious that they completely surround the spiral arteries supplying the mucosal folds of the ampulla and the fimbriae. Many of the mucosal lymphatics bear valves. These vessels drain by channels coursing between the inner and outer layers of the muscle coat.

Lymphatic sinuses are present in the thyroid gland which are readily demonstrable in the newborn [Kulenkampff (68)]. The extent of these endothelial spaces is demonstrated by models made by wax reconstruction. Lymphatics draining the vulva are unusually abundant. Their direction of flow is discussed by Way (69) with reference to their surgical importance when involved in carcinoma.

Lymphatic response to injection.—By employing a method of injection of Gerota's fluid in man, it is possible to trace the various lymphatic systems joining the prostate, seminal vesicles, and bladder at superficial and deeper levels [Tesoriere (70)]. Other methods are described for injecting the lymphatic system [Quagliotti (71)]. Best results are obtained with colored gelatin.

The employment of injection pressure not exceeding 120 mm. of India ink into the ventricular and subarachnoid spaces demonstrates regional connection between the space and epidural lymphatics [Brierley & Field (72)]. It appears probable that the dural-arachnoid "cuff" is an area in which both fluid and particles may leave the subarachnoid space to become epidural. Particles not over 1.5μ can pass readily from this space not only into the cervical nodes but into those lying anterior to the vertebral column. These nodes may be regarded as regional lymph nodes for the subarachnoid space. By producing lymphatic abdominal stasis, it is possible to trace fine lymphatics backward from the cisterna chyli [Field & Brierley (73)]. Lymphatic vessels start in the substance of the posterior spinal musculature and pass ventrally in company with nerve and blood supply of the muscle towards the region of the intervertebral foramen. Here fine tributaries reach the lymphatics from the area of the dorsal root ganglia and the arachnoid sac around the nerve roots. The lymphatic continues around the side of the vertebral body to end in one of several valveless longitudinal trunks anterior to the vertebral body. Successful cannulation of a lymphatic of a rabbit produced a retrograde flow into the lymphatic capillaries of the dorsal roots. Particles could be seen passing through the lymphatic wall in closest relation to the nerve just beyond the spinal ganglion [Field & Brierley (74)]. Such lymphatic connections must be taken into account in evaluating clinical and experimental phenomena met with in poliomyelitis. Intraneural injections of the sciatic nerve reach the central nervous system or the subarachnoid space via interfiber spaces or the blood stream directly; lymphatics are not involved [Brierley & Field (75)]. These observations have a direct bearing on the explanation of pathways followed by the

experimental production of a disease by intraneural injection of toxin or virus.

In a study of serial sections of the kidney in a case of unusually extensive lymphatic permeation by carcinoma, Rawson (76) traces two lymphatic systems. The cortical lymphatics begin blindly in contact with Bowman's capsule and form extensive periarterial and perivenous networks running to the corticomedullary junction. The medullary lymphatics also begin blindly, below the papillary epithelium, and run nearly straight to the boundary zone becoming confluent about the arcuate vessels. These observations are at variance with those of Kaiserling (77), who states that the lymphatics are not related to the blood vessels within the renal parenchyma of the rabbit.

A new method for demonstration of both the distribution and functional status of blood and lymphatic vessels by means of the intravenous injection of a fluorescent dye, thioflavine-S, is described by Schlegel (78). The dye first accumulates in the walls of blood vessels, diffusing out into the tissues in 1 or 2 min. Somewhat later the dye reaches the lymphatics. At this time, the vessels appear black against the bright fluorescence of the lymphatic endothelium which has taken up the dye selectively. The progress of this phenomenon may be halted at any stage by freezing the tissue instantly *in situ*. The rate of absorption by lymphatics can be determined if the interval between the injection and fixation is varied. The rapidity of the appearance of the dye in the lymphatics under the above circumstance parallels the results obtained when radioactive iodine (I^{131}), injected intravenously, is recovered in the thoracic duct within 7 to 10 min. [Wasserman & Mayerson (79)]. Similar results are reported by Krieger *et al.* (80). Sizable amounts of I^{131} appear in thoracic duct lymph within 15 to 20 min. [Friedlander *et al.* (81)]. Within 30 min., it can be collected from the lymphatics of the hind leg of the dog.

Injections of the lymphatics draining the anus and rectum of still-born infants reaffirm the observations of others who divide the plexuses into inferior, middle, and superior groups on the basis of the course and termination of the channels draining them [Blair *et al.* (82)]. The inferior region, consisting of the anal canal and the perianal skin, is drained by channels leading to the superficial inguinal nodes; no continuity through the mucocutaneous line could be identified. The lymphatics of this region can be displayed by puncture injection of a dye into the submucosa of the rectum of the dog [Brockman & Krahll (83)]. Within 24 hr., the dye is concentrated in the lymph nodes which receive the rectal drainage. A second injection, made a few hours previous to the exploration, makes the afferent lymphatic vessels visible. This procedure is suggested to facilitate dissection done at operation for rectal carcinoma in the human subject.

Coincidentally, Weinberg & Greaney (84) applied the above suggestion to the human patient, although not in the region suggested. After the abdomen is opened in cases of suspected carcinoma of the stomach, 4 or 5 cc. of

a 2 per cent solution of Pontamine sky blue is injected into the muscularis near the greater and lesser curvatures. The dye is taken up quickly, permitting the identification of small remote nodes adjacent to the larger regional ones. According to the toxicity criteria of Hodge & Steiner (123), Pontamine sky blue is a slightly toxic material [Weinberg *et al.* (85)]. An *in vivo* method of coloring the lymph nodes draining the region of the uterine cervix may be employed preoperatively to insure the visualization of all nodes involved [Zeit & Wilcoxon (86)]. A solution of India ink is injected under the mucosa, maximum coloring appearing 8 hr. later. Instillation of a solution of trypan blue or T1824 into the nose, outlines the lymphatic path to the cervical chain of nodes and indicates the actual functioning of this pathway [Yoffey (87)].

LYMPH NODES

Recent anatomical studies.—A careful statistical analysis of data reveals that in general male mice have larger superficial lymph nodes, larger spleens, and more total lymphoid tissue but smaller thymuses than females [Robertson (88)]. A distinction should be made between the hilar and medullary portions of the capsule of the lymph node [Furuta (89)]. The thicker portion covering the hilar region should be defined as consisting of areolar connective tissue, distinguishing it from the dense fibrous tissue of the rest of the capsule. In hyperplasia of the lymph node, the capsule shows areas of disintegration, and the hilar region shows migration of parenchyma [Furuta (90)]. Under experimental conditions lymph nodes in the rat can be converted gradually into hemolymph nodes by the influence of a prolonged treatment with a carcinogenic agent [Lasnitzki (91)].

Mitotic activity diminishes in lymph nodes of the rat in proportion to increasing age [Andreasen & Christensen (92)]. Relatively normal human lymph nodes, like the normal lymph nodes of rabbits and guinea pigs, do not contain cells morphologically identical with myeloblasts of the bone marrow [Sundberg (93)]. The hemopoietic reticular cell functions as a stem cell for lymphocytes, and the myeloblast functions as the stem cell for myeloid elements. These observations are in accord with Harris & Harris (94). Complete accord does not exist on these statements. Farr (95), on the basis of intravenous injections of labeled lymphocytes, suggests that lymphocytes which leave the blood stream go either to lymphatic tissue to give rise to lymphocytes or bone marrow where they can transform into cells of the granulocytic series. Variations occur in the time of maturity of the developing lymphoid tissue in the newborn to the thirty-fifth day guinea pig [Gyllenstein (96)]. The maturity decreases in the following order: Peyer's patches and cervical lymph nodes, lymph nodes of extremities, tracheal and mesenteric lymph nodes, and white splenic pulp.

Injection of nitrogen mustard or formalin reduces the weight of lymphoid tissue of the mouse [Robertson (88)]. Adrenalectomy protects against the involution induced by formalin but affords little protection against that

by nitrogen mustard. The histologic effects on lymphatic nodules of the rabbit after x-rays and after nitrogen mustard are identical in nature, but there is a quantitative difference in response [DeBruyn & Robertson (97)]. Exposure to repeated injections of insulin causes a reduction in the weight of lymphatic tissue in rats [Zeckwer (98)].

Acid colloidal pigments injected intraperitoneally, depending on their degree of toxicity, will affect the pattern of phagocytosis and lymphogenesis of the nodes [Baillif (99)]. Intravenous injection of a suspension of cellular constituents from lymph nodes into adult rabbits result in a focal accumulation of lymphocytes in the radicals of the interlobular portal vein, periportal spaces of the liver, small vessels of lymph nodes, and in the perifollicular regions of the spleen [Osogoe (100)]. Similar results are obtained by the injection of cellular elements of bone marrow [Osogoe & Omura (101)].

Effect of irradiation on lymph nodes.—The extent of histological damage found in lymph nodes of animals exposed to x-rays is correlated with the dose of x-rays [DeBruyn (102)]. Lymph nodules regenerate after their elimination by irradiation. No morphological damage to the reticuloendothelial system results from a single whole body radiation of medium dosage in the mouse [Brecher *et al.* (103)]. By injecting lymphatics directly with a radioactive colloid (yttrium), it is possible to irradiate nodes receiving the lymph [Walker (104)]. An increase in uptake of colloid by these nodes occurs after subsequent injections. Of the lymphoid tissues, nodes show the most profound depression, appearing later and lasting longer after radiation injury resulting from the injection of various dosages of P^{32} [Warren *et al.* (105)]. By 84 days, lymph nodes of mice still are not completely restored but continue to show scant proliferation begun at 15 to 20 days after injection. Although restoration of lymphoid tissue and bone marrow is accomplished, some animals die because of radiation injury. This apparently indicates an irreparable generalized injury which cannot be adequately demonstrated morphologically but causes death despite well developed regeneration of these most radiosensitive tissues [Warren & Dixon (106)].

Endocrine influence on lymphatic tissue.—The administration of thyroxin to adult male mice results in an increase in the organ weight of the peripheral lymph nodes, kidneys, and spleen according to Mader (107). This phenomenon is not obtained from studies on the rat, where Feldman (108) finds that the thyroid has no apparent effect. Administration of growth hormone to hypophysectomized male rats results in marked proliferation and hypertrophy of lymphoid cells, whereas hypophysectomy alone is followed by atrophy of both organs and cells. Adrenalectomy results in hyperplasia and hypertrophy of lymphoid tissue. Mader (107) concurs with this later statement. Moon *et al.* (109) do not agree that administration of pure pituitary growth hormone increases the amount of lymphoid tissue, except in the peribronchial area of female rats. The combined action of a small dose of cortical extract and nonspecific stress of moderate intensity has a marked caryoclastic effect on the lymphoid system of adrenalectomized

rats, while the same dose of extract given to adrenalectomized, nonstressed rats produces a negligible effect [Herlant (110)]. The lymphoclastic effect is produced by a single injection of 10 mg. desoxycorticosterone acetate in rats not only in lymph nodes but in the blood picture [Akert *et al.* (111)]. The same effect, only more impressive, takes place under the influence of pituitary adrenocorticotrophic hormone. Adrenocorticotrophin or cortisone produces a temporary shrinkage of enlarged lymph nodes, spleens, and livers when given to patients with chronic lymphatic leukemia, lymphosarcoma, acute lymphatic leukemia, and acute granulocytic leukemia [Pearson & Eliel (112) and Pearson *et al.* (113)]. A slight shrinkage of enlarged lymph nodes and spleens is observed in patients with Hodgkin's disease during hormone administration. A marked retardation of tumor growth rate without completely inhibiting absolute growth occurs after a 48-hr. fast in tumor bearing (transplantable lymphosarcoma) CBA mice [Adams & White (114)]. The tumor growth differential is not dependent on the presence of adrenals. However, nonmalignant lymphoid structures in tumor-bearing animals show the same involutinal effect of fasting and the same dependence of this phenomenon on the presence of adrenals as has been reported for tumor-free animals. Treatment of mice with x-rays, aminopterin, and adrenocorticotrophic hormone increases poliomyelitis infections following intraperitoneal injection of MEF strain virus [Sommers *et al.* (115)]. This is ascribed to the damage to the lymphoid tissues produced by these agents.

Miscellaneous.—After the cells of C3H mammary carcinomas and lymphosarcomas are implanted subcutaneously in racially-resistant mice, lymph nodes of the hosts become markedly hyperplastic. The number of germinal centers increases and a great thickening of the medullary cords results from proliferation of elements that seem to be young plasma cells which mature later [Ellis *et al.* (116)].

Inoculation of the foot-pad of the rat with *Pneumococcus* produces changes in the popliteal node within 5 min. [Smith & Wood (117)]. The first change is a dilatation of the sinuses. When the inflammatory reaction is well advanced, great concentration of polymorphonuclear leucocytes is seen at the hilar portions of both intermediary and subcapsular sinuses. This would seem to enhance the filtration power of the node. Macrophages invade the nodal sinuses later, probably constituting a late phase in the recovery of the inflamed node. The polymorphonuclear leucocytes in the nodal sinuses originate both from blood vessels of the node and from the primary inflammatory focus in the tissues [Smith & Woods (118)].

Extensive extirpations of approximately 90 per cent of organoid lymphoid tissues in rats do not influence significantly the normal range of serum proteins. This would seem to dispose of the lymphoid organs as an essential factor in serum protein production in this animal [Andreasen *et al.* (119)].

Resection of mesenteric lymph nodes in dogs does not alter fecal fat and nitrogen excretion [Clarke *et al.* (120)]. A rapid re-establishment of anatomic and functional continuity of the interrupted mesenteric lymphatics and, in some animals, a partial regeneration of nodes occurred.

The segregation of dispersed cellular particles obtained from human lymph nodes can be carried out using a 10-step centrifugation procedure and a fluid medium [Hoster *et al.* (121)]. Analysis of particles ranging from 10 to 280 $m\mu$ found in high gravity segments of neoplastic and nonneoplastic node suspension on electron microscope examination indicates that the small particle population is polydispersed. The predominance of particles 10 to 20 $m\mu$ in the Hodgkin's lymph node sediments and the lack of a predominant size range in the nonneoplastic lymph node sediments are statistically significant.

Slices of popliteal lymph nodes from rabbits, when placed on exposed surfaces of the chorioallantoic membranes of the developing chick embryos, show the following changes after four days incubation [Harris & Harris (122)]. Vascularization extended in the direction of the rabbit tissue which was undergoing degeneration, reticulum cells appeared in lymph nodes, and on occasion mature lymphocytes appeared.

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THE KIDNEY¹

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This review ends a period of publication which might be termed "The Year of the Kidney." Wolf's text on urinary function (1) deals principally with concepts and kinetics of fluid and electrolyte excretion; the Macy Conference (2) on the kidney tells a great deal about the investigators and much that is new in investigation; clinically oriented seminars appeared in series in the *American Journal of Medicine* (3); the culmination was Homer Smith's text (4), a volume historically comparable to Cushny's *The Secretion of the Urine*.

ANATOMY²

Neoprene injection in normal human kidneys demonstrated no pre-glomerular shunts and no arteriovenous anastomoses. Arteriolae rectae verae were rare enough to minimize their physiological significance. The only vessels through which blood might circulate in large amounts when diverted from the cortex were those of juxtamedullary glomeruli, their efferents, and vasa rectae [More & Duff (9)]. Pease & Baker (10) showed that glomerular capillary endothelium is discontinuous; the visceral epithelium may be continuous. The relatively thick basement membrane which lies between is ridged and ribbed on its visceral surface, an arrangement which makes for increased resistance to bursting pressures and may account for dispersal of porosity. Gautier, Bernhard & Oberlin (11) suggested that capillarity of these ridges may be a regulatory factor in filtration. The endothelium of peritubular capillaries is seemingly discontinuous. The brush border of proximal tubule cells is composed of finger-like processes which greatly increase the active surface. Dalton *et al.* (12) showed that these filaments arise below the cell surface. They confirmed Pease and Baker's demonstration of interdigitations of proximal tubular cells and showed that their cell membranes are discrete.

THE GLOMERULUS AND PROTEINURIA

Handler & Cohn (13) seem to have shown that the glomerulus is freely permeable to normal concentrations of serum inorganic phosphate. Marshall and Deutsch (14) have studied in dogs the ratios to creatinine clearance (C_{Cr}) of clearances of proteins of varying molecular size. Lysozyme, the smallest molecule, was excreted more rapidly than other egg-white proteins. Clearances of ovomucoid and ovalbumin were equal at about 15 per cent of creatinine clearance. The molecular weight of ovomucoid is less, but its molecule may be more asymmetrical. Clearance of β -lactoglobulin depended

¹ The survey of the literature pertaining to this review was concluded in June, 1951.

² See also references (5 to 8).

in part on serum concentration. Glomerular porosity seemed to vary with molecular size, but the relationship was obscured by complex formation between injected and circulating proteins and by tubular reabsorption. One study [McDonald, Miller & Roach (15)] indicated that glomerular porosity to injected hemoglobin in human beings is about 12 per cent that of inulin. The estimate seems high. Tubular recovery of hemoglobin averaged about 17 mg. per min. per 100 cc. of glomerular filtrate. In proteinuric patients, Brandt, Frank & Lichtman (16) found that the ratio hemoglobin clearance/inulin clearance (C_H/C_{In}) was in the range of 0.02 to 0.05 at serum levels of hemoglobin up to 5.5 mg. per ml. and increased when infusion was prolonged. Since the ratio is about the same in normal subjects, it seems that increased glomerular porosity to macromolecules of the size of hemoglobin is not the cause of proteinuria. In this connection, Corcoran (17) has shown that in normal people glomerular porosity, defined as the ratio, levan clearance/mannitol clearance (C_L/C_M) is 1:1, and that the ratio decreases in hypertension and is lower still in glomerular disease. Levan is a grass polysaccharide, of molecular weight about 8500. Porosity decreases as proteinuria increases in patients with glomerular disease, which suggests that their proteinuria is primarily glomerular. That tubular factors intervene in proteinuria was demonstrated by Lippman, Ureen & Oliver (18, 19). Proteins, including renin, act on excretion of hemoglobin by the rat. Lippman *et al.*, proposed the concept that there are two mechanisms of tubular transport of hemoglobin. The one is "direct" and does not involve vacuole formation; the other "indirect" pathway does. Renin interferes with direct transport across the cell. Kidneys of male rats excrete more protein than females [Sellers *et al.* (20)]. Castration of males reduces proteinuria; testosterone increases protein excretion in male and female castrates. Proteinuria induced by renin in rats [Marmorston *et al.* (21)] is increased by adrenocorticotrophin (ACTH). Proteinuria in human beings with glomerulonephritis is sometimes relieved by treatment with nitrogen mustard [Chasis, Goldring & Baldwin (22); Taylor, Corcoran & Page (23)]. However, proteinuria induced by intraperitoneal injection of albumin in rats was increased by injections of HN_2 [Lippman & Ureen (24)]. Both glomerular and tubular factors seem to intervene in exercise proteinuria in human beings [Javitt & Miller (25)]. In pregnancy the excretion curve of another protein, gonadotrophin [Loraine (26)], increased during the first trimester and subsequently decreased. It was high in the last trimester in pregnant diabetic women and in severe pre-eclampsia. Gonadotrophin clearance remained somewhat under unity throughout pregnancy so that increased outputs in pre-eclampsia and toxemia were referable to increased serum concentrations of hormone.

GLOMERULAR FILTRATION

In the rat we [Corcoran, Masson, Reuting & Page (27)] had found under specific conditions that the clearance of exogenous creatinine (C_{Cr} exogenous) was the same as that of inulin. Martel, Wang & Gingras (28), impressed by

the effect of hexahomoserine in stimulating creatinine output, found that in rats, as in man, creatinine clearance is in part a tubular excretory function. This function is stimulated by hexahomoserine. In rabbits, glomerular filtration rate (GFR) and urine flow were again found to be interdependent [Dicker & Heller (29)]. Ferrocyanide, like creatinine, had been assumed to be entirely excreted by filtration but actually undergoes a more complex excretion in the cat [Eggleton & Habib (30)]. At low concentrations its clearance is less than filtration rate, and at high concentrations it exceeds that of creatinine; thus it seems to be excreted by filtration, by reabsorption at the rate of about 10 mg. per 100 cc. of glomerular filtrate, and then by tubular excretion which increases as serum concentrations rise. Tubular reabsorption of urea is depressed by administration of *p*-aminohippuric acid (PAH) at tubular maximum (Tm) concentrations [Dern & Pullman (31)] and stabilized by sodium thiosulfate [Effersøe (32)], presumably as a result of diuresis.

TUBULAR TRANSPORT

This topic has been generously reviewed during the past year by Beyer (33) and by Taggart (34). Noteworthy is Beyer's statement that "in principle, the measurement of the functional capacity of a renal transport system is identical with that for the assay of an enzyme in terms of its functions." Tubular transport systems were envisaged as "complex enzymatic systems that, in addition to having specificity, are involved in a spatial transport of materials that is oriented directionally." Inhibitions of transport systems are discussed in relationship to enzyme chemistry. Specific attention was given the action of Carinamide (4'-carboxyphenylmethane sulfonanilide) and Benemid on tubular transport of PAH and the hypothesis presented that they act "on the definitive conjugase of the reaction involved in synthesis of PAH from PAB or of PAHX (the intermediary conjugate) from PAH." Taggart drew particular attention to the effect of dinitrophenol (DNP) in depressing cellular transport of phenol red and PAH. DNP seemed to act by blocking the generation of energy-rich phosphates without depressing respiration of enzymes. Beyer considered that these phosphate compounds facilitate conjugations which determine transport of PAH and similar compounds. Taggart directed attention to the participation of acetate in the transport mechanism; Beyer considered that acetate and conjugase participate in the same reaction. It is difficult to reconcile the lack of effect of DNP on tubular reabsorption and the pronounced effect of phloridzin, also assumed to act on high energy phosphate bonds, on both reabsorptive and excretory mechanisms.

Judah & Williams-Ashman (35) have described enzymes that catalyze esterification of inorganic phosphate and oxidation of glutamine in mitochondrial fractions of liver and kidney. DNP stimulation of oxidation of glutamine by kidney particles depends on fluoride. Catalysis of acetate oxidation by kidney particles is inhibited by substances such as DNP which disrupt the linkage between oxidation and phosphorylation. Oxidation of

acetate may be a limiting factor in the free flow of Beyer's conjugase system. Stoneham *et al.* (36) have shown in the dog that both dehydroacetic acid and Carinamide depress tubular maximum of *p*-aminohippurate (Tm_{PAH}) and that this depression is reversed by provision of acetate. Restoration of phenol red excretion required more acetate than was needed for recovery of Tm_{PAH} . This behavior of phenol red and its lower extraction ratio (Er) indicate that it has less affinity for transport receptors than has PAH, possibly because of protein binding. Benemid, Carinamide, cinchonic acids, ethylene-diamine derivatives, and other enzyme inhibitors show a general parallelism in their effects on phenol red and PAH transport [Beyer *et al.* (37)]. Zubrod *et al.* (38) have shown that 3-hydroxy-2-phenylcinchonic acid acts like Carinamide and has a clearance of about 0.05 cc. per min. in the dog. Benemid has been shown not to decrease glucose phosphorylation by phosphorylase plus adenosinetriphosphate [Beyer *et al.* (39)]. It delays the excretion of penicillin and to some extent of *p*-aminosalicylic acid, but has no effect on blood levels of aureomycin, chloromycetin, streptomycin, and terramycin [Boger *et al.* (40)].

That reabsorptive mechanisms in renal tubule and intestine are similar was suggested by Bogdanove & Barker (41), who found that phloridzin inhibits intestinal absorption of glucose, galactose, and possibly mannose and sorbose in rats, but not of fructose. A phloridzin-like action of desoxycorticosterone glucoside has been suggested because of the glycosuria it causes [Green *et al.* (42)]. Desoxycorticosterone acetate (DCA) is without effect on glucose tubular maximum (Tm_G) [Wirz (43)]. Some adrenal cortical influence on glucose reabsorption is suggested by the observation that both GFR and Tm_G decrease in adrenalectomized dogs. GFR can be restored to normal by saline infusions; Tm_G persists at low levels from which, with long-continued treatment with DCA, it can be restored to normal. The onset of glycosuria during treatment with ACTH has been demonstrated to be in part renal; it was associated with depression of Tm_G in two patients with severe hypertensive disease [Dustan, Corcoran, Taylor & Page (44)]. Holton & Lundbaek (45) consider it to be both renal and metabolic. Lambert *et al.* (46), who used small doses of ACTH over short periods, did not demonstrate a change in Tm_G or in renal threshold. Cortisone somewhat depressed Tm_G in one of our patients. Cortisone glycosuria in rats is not renal [Lazarow (47)].

Farber, Berger & Earle (48) found that intravenous insulin depressed Tm_G in 12 diabetics and in two of four normal subjects. The ratio, GFR/Tm_G was significantly decreased in diabetics, which indicated a facilitation of glucose reabsorption. Govaerts (49) has demonstrated that, if urinary glucose be taken as the ordinate and blood sugar as the abscissa, their relationship indicates two glucose "thresholds." The "appearance" threshold is that point at which nephrons with the lowest Tm_G 's become saturated; the second threshold, beyond which the relationship between urinary glucose and blood sugar becomes linear, is the point at which all nephrons are saturated and corresponds to Tm_G . This is in effect a clinical application of the splay of Tm_G .

Renal gluconeogenesis occurred in the intact dog at the rate of about 60 mg. per kg. body weight per hr. [Cohn, Katz & Kolinsky (50)]. The indicated arteriovenous difference corresponds with the mean of 2 mg. per 100 cc. of blood found by Clark (51) in human beings. Renal gluconeogenesis was increased by hyperglycemia in dogs. This glucose did not arise from renal glycogen [Cohn, Katz & Cohn (52)] since renal glycogen was increased in eviscerated, hepatectomized dogs. Renal glucogenesis in rabbits occurred only after hepatectomy and during hypoglycemia and did not add effectively to total body glucose [Drury, Wick & MacKay (53)].

In man, simultaneous clearances of inulin and urate indicated active reabsorption of urate at the rate of about 15 mg. per min. per 1.73 sq. m. The normal presence of urate in urine indicates that it, like phosphate, amino acids, and ascorbic acid, is excreted without saturation of the reabsorbing mechanism [Berliner *et al.* (54)]. Gutman (55) has reviewed the physiology of gout and noted the uricosuric effects of Carinamide and Benemid. Suppression of urate reabsorption by these benzoic acid derivatives and their lack of effect on other reabsorptive functions suggest that urate reabsorption somehow involves the system postulated by Beyer for reabsorption of *p*-aminobenzoic acid. The uricosuric effect of Diodrast is also directed at this mechanism; uricosuria by salicylate or mercurhydrin are presumably different [Miller, Danzig & Talbott (56)]. None of these agents affected uric acid output of the Dalmatian dog [Friedman & Byers (57)]. Uricosuria in this species is a renal phenomenon due to lack of renal urate reabsorption and not to an abnormality of tissue metabolism. In the rat [Friedman & Byers (58)], ACTH caused an increase in urate excretion without change in GFR as measured from $C_{\text{Allantoin}}$ or C_{Cr} . ACTH was without effect on the rate of accumulation of blood urate in the nephrectomized rat; ACTH uricosuria seems to depend on slowed tubular reabsorption. Secretion of urate has been demonstrated in a hypouricemic man [Praetorius & Kirk (59)].

At least two reabsorptive mechanisms are involved in amino acid reabsorption [Beyer (33)]. One is concerned mainly with the basic amino acids and is demonstrated by reabsorptive competition between arginine, histidine, and lysine; a second deals with the monoamino-monocarboxylic acids, leucine and isoleucine. A third may be concerned with reabsorption of glycine which competes with creatine. Kamin & Handler (60) found that infusion of one amino acid in dogs considerably increased outputs of amino acids of similar acidic properties. More glutamic and aspartic acids appeared in the urine than could be accounted for by glomerular filtration (although GFR was not measured), so that nonessential amino acids may be excreted in part by tubular secretion. The excretions of histidine and threonine were disproportionately increased by infusions of other amino acids. No simple scheme of mutual competition could be established.

ACTH and cortisone are known to accelerate protein catabolism during which aminoaciduria might reasonably be expected. Brodie *et al.* (61) have shown that administration of these substances to patients with rheumatoid

arthritis caused aminoaciduria of threonine, lysine, and tyrosine. Lysine was little affected by cortisone; neither this nor ACTH affected arginine. A renal effect, like that on urate, was not excluded.

Hogben & Bollman (62) have studied maximal tubular transport of phosphate (Tm_P) in the frog kidney. They found phosphate not subject to tubular secretion. Variations in concentration gradient did not influence Tm_P . They conclude that the limiting factor is not intracellular, but that the cellular membrane acts by "adsorption semipermeability," and suggest that this function may extend to other substances subject to limited reabsorption. They also found (63) an unstable, apparently exhaustible reabsorptive Tm_P in dogs. Thyroparathyroidectomy often increased reabsorption of exogenous and endogenous phosphate. Parathyroid extract induced phosphaturia [Jahan & Pitts (64)] but did not influence Tm_P . Handler, Cohn & DeMaria (65) have shown that phosphaturia induced in dogs by intravenous administration of parathyroid extract is more dependent on increased tubular phosphate load than on decreased phosphate reabsorption. Crawford *et al.* (66) have calculated the ratio of reabsorbed/filtered phosphate (TRP/GFP) in rats and human beings on the assumption that $C_{Cr \text{ endogenous}}$ equals GFR. In parathyroidectomized animals the ratio is close to unity. It is diminished by administration of parathyroid extract and by increased phosphorus intake. Thus, TRP/GFP seems to vary with parathyroid activity; the corollary is that phosphorus homeostasis depends on parathyroid control of renal phosphorus excretion. In the rat very large doses of parathyroid extract (100 to 200 units) resulted in phosphaturia which increased over 6 hr., without associated changes in renal alkaline or acid phosphatases [Kochakian & Terepka (67)]. Longer treatment resulted in decalcification of bones with metastatic calcification in heart and kidney. Physiological doses (30 to 50 units daily) were without effect on bone or other organ enzymes.

ELECTROLYTES

Berliner (68) considered present knowledge of electrolyte and water excretion "fragmentary." It is. Selkurt & Post (69) demonstrated a distal tubular limiting value of sodium reabsorption (Tm^d_{Na}) in dogs. After hypertonic sodium chloride loading, the curves of increased reabsorption varied individually. Reabsorption decreased in prolonged experiments, probably because of hormonal changes. Prehydration of human beings by establishment of water diuresis left a "trace" effect which decreased reabsorption of an isotonic sodium chloride load, 8 to 13 hr. later [Ladd (70)]. Factors other than filtration and load are believed by Wiggins *et al.* to determine outputs of sodium and chloride (71). Black, Platt & Stanbury (72) found that normal human subjects deprived of sodium by prolonged rice diet developed increased sodium reabsorption that persisted for hours after hypertonic sodium loads had been imposed. Since potassium excretion was not concurrently increased, they did not view the stimulus as desoxycorticosterone-like. They noted parallelism, without equality, of C_{In} and $C_{Cr \text{ endogenous}}$.

New-born infants, whose kidneys are functionally inadequate in many other respects [McCance (73)], respond in an adult fashion to DCA by sodium retention and potassium loss [Klein (74)]. Wirz (75) found that appropriately spaced doses of cortisone cause as much sodium retention in adrenalectomized rats as a single dose of DCA. In such rats, Simpson & Taite (76) have confirmed that DCA (1.5 to 32 $\mu\text{g.}$) causes quantitative increments of sodium retention followed by net loss. Normal rats on salt-poor diets show evidences of adrenal cortical activation without increased urinary 17-ketosteroids [Danford & Danford (77)]. The zona glomerulosa of rat adrenal cortex has been considered to give rise to salt (sodium and potassium) regulatory steroids, independently of ACTH which stimulates secretion of "glucocorticoids" from the zona fasciculata. The zona glomerulosa is hypertrophied in renal hypertension or by prolonged treatment with renin [Deane & Masson (78)]; the latter is known to increase sodium output. However, in dogs, hypophysectomy results in atrophy of all three cortical zones [Lane (79)]. These dogs remain in sodium balance [Surtshin, Rolf & White (80)], handle loads of potassium and retain sodium in a relatively normal manner [Earle *et al.* (81)] in spite of decreased GFR, renal plasma flow (RPF), and TmPAH . Renotrophic preparations of growth hormone, which increase GFR and other functions, do not alter sodium reabsorption (80). Whether on a sodium- and protein-poor rice diet, or during administration of sodium loads, hypophysectomized dogs in osmotic diuresis show normal tubular rejection of sodium [Simmons *et al.* (82)]. Thus, electrolyte control in hypophysectomized dogs seems to be independent of adrenal and pituitary tropic influences, possibly by a compounding of deficiencies.

Evidence of biphasic (hemodynamic: hormonal) control of sodium output in dogs was reported by Wesson *et al.* (83) who found that excretion varied through three phases during expansion of extracellular fluid. In the first, GFR, RPF, and sodium output increased; in the second, sodium reabsorption increased, the urine became dilute, and GFR and RPF tended to return to normal; in the third, GFR and RPF again rose, but sodium reabsorption remained high. Tubular secretion of potassium [Berliner, Kennedy & Hilton (84)] seems to occur by sodium-potassium cation exchange in the distal tubule. Danowski & Elkinton (85) have reviewed potassium metabolism, including renal aspects, and have suggested that content or concentration of potassium in tissue cells is the stimulus of potassium loss; Mudge *et al.* (86) found that dehydration-induced potassium loss is the result of tubular secretion. Dehydration did not elicit potassium secretion by new-born rats [Dicker (87)]. Accumulation of potassium in the kidney tissue slices resulted from active transport. Accumulation from low concentrations was more dependent on tissue metabolism than on physical factors such as osmotic pressure or pH [Mudge (88)]; at high potassium concentrations metabolic activity was less significant; sodium and potassium varied reciprocally. Dietary potassium deficiency had effects comparable to DCA overdosage. Dogs developed polyuria and polydipsia which increased over three to seven weeks

and then tended to subside, the onset of which preceded paresis and spasticity [Smith & Lasater (89)]. Rats on potassium-deficient diets developed increased kidney and adrenal weights [Fuhrman & Brokaw (90)] and hypotension [Freed & Friedman (91)].

Reabsorptions of sodium and potassium are reciprocally depressed in dogs [Baldwin, Kahana & Clarke (92)]. Anions do not show this specificity. Rapoport & West (93) have shown a reproducible relationship of urine volume and solute load with a complete absence of anion antagonism or specificity under varying loads (SCN^- , NO_3^- , HCO_3^- , SO_4^- , $\text{S}_2\text{O}_8^{2-}$, $\text{Fe}(\text{CN})_6^{4-}$, PAH, and mannitol). The authors concluded that the site of ion interaction is proximal "to the point in the tubule where the final urinary load is determined and below which only water reabsorption occurs." This conclusion suggests that effects of serum chloride and bicarbonate concentrations on chloride reabsorption [Pullman & McClure (94)] are exerted in the proximal tubule. Rapoport & West (95) found also that sodium and potassium outputs increase (sodium to 33 per cent of filtered level and potassium to 95 per cent) with the valence of loading anions. They emphasize [West & Rapoport (96)] that the solute load is the determinant of urine volume. Kaplan & Rapoport (97) observed that unilateral splanchnicotomy in dogs resulted in increased homolateral outputs of sodium and chloride under Rapoport's test conditions (hydropenia, osmotic loading) and concluded that renal nerves have some specific effect on proximal tubular reabsorption. Radomski *et al.* (98) found that lithium in dogs induced loss of sodium, retention of potassium, and terminal azotemia and hyperkalemia. Distal and collecting tubules showed regeneration, atrophy, and occasionally, necrosis. Milder lithium intoxication was independent of renal failure or hyperkalemia [Corcoran, Taylor & Page (99)].

Mercurial diuresis was believed to be coincident with depression of renal succinic dehydrogenase [Handley & Lavik (100)]; the depression is abolished by administration of British antilewisite (BAL). However, Fawaz & Fawaz (101) were unable to confirm this relationship. *In vitro* studies indicated the mercurials act by losing mercury to some renal dithiol which tends to exchange it with BAL [Lehman *et al.* (102)]. The view that mercurial diuretics act in the distal tubule as a result of concentration was contested by Farah, Cobbey & Mook (103), who pointed out that in dogs mercurials increase the ratio urine sodium/plasma sodium (U/P Na) to levels greater than unity, that sodium output reaches a maximum before water does, and that BAL inhibits water output before it affects sodium. Tarail & Mateer (104) found that Mercuhydrin (meralluride) increased urine volume and electrolyte output in human beings with diabetes insipidus and that pitressin only partly prevented the increase in water output. None of these observations exclude the possibility of mercurial action on some discrete point in the distal tubule. The effect of mercurials on potassium output was biphasic and dependent on load: they depressed potassium output during potassium chloride loading and increased it during water diuresis [Mudge *et al.* (105)]. The assumption

that mercurials depress both potassium reabsorption and potassium secretion resolves the paradox. Iseri, Boyle & Myers (106) found that mercurial-induced fluid loss in cardiac failure is such as to suggest a shift of potassium from cells and of sodium into them. Extrarenal dependence of mercurial diuresis on intact biliary flow is illusory [Pratt *et al.* (107)].

Effects of altered renal circulation on sodium output in dogs have been examined from the heart to the kidney and back. Levy (108) decreased cardiac output by partial occlusion of the pulmonary artery and found a decrease in sodium output in proportion to tubular sodium load. Decreased cardiac output due to acute pericardial effusion [Post (109)] caused disproportionate depression of sodium output, decreases in RPF and GFR, and increases in central venous pressure, peripheral resistance, and renal fraction. Davis, Lindsay & Southworth (110) observed the course of acute and chronic cellophane pericarditis. Sodium retention occurred in two phases: in the acute phase, there was generalized edema and decrease in RPF and GFR; the chronic phase began at about 10 days and continued for months, during which the clearances returned to normal and ascites replaced edema. Plasma volume and venous pressure were increased and sodium and chloride were retained in both phases. Sodium retention in the acute phase was associated with decreased sodium load; this factor was not evident in the chronic phase. Increased venous pressure was common to both.

Renal arterial pressure was progressively decreased by intra-aortic balloons [Thompson & Pitts (111)]: renal blood flow (RBF) and GFR decreased at pressures of 90 mm. Hg or less, and water and sodium outputs were severely depressed. Constriction of the renal artery caused prolonged homolateral decreases in sodium and water outputs, which, in some of the experiments of Mueller *et al.* (112) seemed to be independent of GFR, although the authors "take the position that slight falls in GFR did occur." Arterial pressures were not indicated, although the method is one which might result in renal hypertension. In dogs with hypertension caused by partial renal arterial compression from metal clamps, Stamler, Hwang & Kuramoto (113) could not show noteworthy changes in responses to sodium and chloride loads, which reaction corresponds with the resistance of dogs with perinephritic renal hypertension to sodium restriction [Page & Lewis (114)].

On the venous side, Hall & Selkurt (115) found, in brief experiments, that graded increments of renal venous pressure to levels of 20 to 30 cm. H₂O decreased sodium clearance and urine volume proportionally, possibly by increasing iso-osmotic reabsorption; increments of pressure to 30 cm. H₂O depressed GFR and increased potassium U/P ratio. Potassium secretion may have been stimulated at the same time as potassium reabsorption. A link between the effects on sodium output of these hemodynamic changes, any of which might damp intrarenal pulsation, was Selkurt's observation (116) that decreasing the renal arterial pulse to 90 mm. Hg had no effect on C_{PAH} and little on C_{Cr} ; severe decreases in outputs of sodium and of water resulted; decrease in pulse pressure had no distinct effect on any of these functions.

This does not confirm Gesell (117) who found that decreased pulse pressure did not affect creatinine output but did depress excretion of water, chloride, and urea. Light pentobarbital anesthesia was used in many of the experiments cited above. Selkurt & Glauser (118) reassuringly found that it has a negligible effect on dogs' responses to increased sodium loads.

Decreases in GFR and sodium output in normal human beings during quiet standing have been attributed to decrease of circulating plasma volume; however, Epstein *et al.* (119) found that restoration of plasma volume by infusion of albumin and of GFR by hypertonic sodium chloride does not prevent a decrease in sodium output. In dogs, bleeding tended to decrease sodium output [Netravisesch & White (120)], but neither bleeding nor transfusion altered responses to test doses of sodium chloride. A study of the effect of posture on sodium output in human beings has been extended by Lombardo *et al.* (121): in the sitting position, removal of small amounts of blood decreased sodium output without changing GFR and RPF; compression of the neck prevented the effect on sodium. In recumbency, sodium output could only be decreased by removal of larger volumes of blood; this effect was not prevented by neck compression. They suggest that, apart from recognized hemodynamic and hormonal controls, the blood content of the cerebrum somehow affects sodium output.

THE RENAL BLOOD FLOW

Interrelationships of renal blood flow and electrolyte output account for a seemingly belated consideration of this topic. Papers by Burton (122), Nichol *et al.* (123), and Guyton *et al.* (124), although not directly related to the renal circulation, bear so closely on the physiology of small vessels as to recommend their study. The former two are concerned with intrinsic physical equilibria and the latter with autonomic regulatory mechanisms. Experimental polycythemia decreases RPF, while RBF, GFR, and over-all renal resistance are well maintained (afferent and, possibly, efferent vasodilatation) [Spencer (125)]. In severe chronic anemia [Paterson (126)] RBF and GFR decrease and renal resistance rises; T_{mPAH} and T_{mG} are maintained. The change in flow, possibly the result of perfusion of fewer glomerular capillaries, is not the result of anoxia, since prolonged hypoxia increases RPF and GFR, also without affecting T_{mPAH} [Marshall & Specht (127)].

Brull & Louis-Bar (128), confirming earlier observations, found that RBF of isolated kidneys is increased by increases of arterial pressure; changes in urine flow paralleled changes in arterial pressure more closely than venous blood flow. At 300 mm. Hg, induction of diuresis (urea or caffeine) increased intrarenal pressure, split the capsule, and disorganized what renal function there was. Under more physiological conditions, Shipley & Study (129) altered perfusion pressures of one kidney of a dog in the range, 20 to 320 mm. Hg. Urine flow began at about 60 mm. Hg and rose exponentially until, at the highest pressures, it amounted to two-thirds of GFR. Study & Shipley (130) found that RPF, GFR, and ER_{PAH} increased rapidly

from 60 to 80 mm. Hg, and stabilized up to 180 mm. Hg; above this pressure RBF increased sharply and inulin extraction ratio (Er_{In}) fell. They detected addition of a creatinine-like chromogen to renal venous blood at low perfusion pressures.

Maxwell, Breed & Smith (131) have summarized their own and others' data to the effect that, in man, the juxtamedullary circulation does not act as a true shunt. One opposing note arises from disparities of extraction ratios of mannitol and PAH elicited by histamine and epinephrine in human subjects [Reubi *et al.* (132)]. However, small analytical errors compound in calculations of RBF from clearances and instantaneous extraction ratios. Even in rabbits, Schlegel & Moses (133), using a refined technique of intravital staining with Thioflavine S, a dye which outlines arteries and glomeruli in ultraviolet light, found no evidence of shunt from leg crushing, nor did stimulation of renal nerves elicit shunts in rats, rabbits, or dogs [Block, Wakim & Mann (134)]. Scher (135), estimating changes in blood flow from changes in intrarenal temperatures, found that arterenol, epinephrine, acetylcholine, and stimulation of renal nerves all decreased blood flow concurrently in medulla and cortex. Maluf (136), used india ink as a marker and found no selective cortical ischemia in dogs (splanchnic stimulation, epinephrine, histamine, limb tourniquets) nor, in rabbits, from injection of incompatible blood. Circulation time through the kidney was relatively independent of arterial pressure, blood flow, or resistance [Bruner *et al.* (137)], which is consistent with the existence of low resistance shunts, such as those which transmit glass spheres. It is speculatively possible [Trueta (138)] that potential cortical ischemia may be a factor in some forms of hypertensive disease; but cortical and medullary circulations have no intrinsic dependence [Lamport (139)].

Related to shunting is intermittence of nephron function which has not generally been considered normal except in the rabbit; this view is sustained in part by constancy of Tm_G/GFR in renal hyperemia and ischemia in man. However, changes in GFR in dogs concurrently change Tm_G [Moyer & Handley (140)], and heat stress has similar effects [Pitesky & Last (141)]. Selkurt & Post (69) attribute the increases in GFR during hypertonic sodium chloride loading in dogs to the bringing into function of inactive nephrons or capillaries. The effects of hypophysectomy and growth hormone preparations in dogs might be similarly adduced, as also the effects in this species of protein feeding and restriction. Thus, the weight of evidence favors nephron or glomerular capillary intermittence or both in dogs, but this species has a notably labile renal blood flow.

Calculations of renal vascular resistance usually assume an intrarenal pressure of about 10 mm. Hg, based in large measure on Winton's studies (146). Swann *et al.* (142), using needle punctures, estimate this pressure at about 25 mm. Hg and find that the same holds for rabbits and dogs [Montgomery *et al.* (143)]. Occlusion of the renal vein increases intrarenal pressure as venous pressure rises above this level; the two pressures then rise concur-

rently to somewhat less than diastolic pressure. Gottschalk (144), using a technique which seems better adapted for the purpose, found intrarenal pressures of the order of 10 mm. Hg in pigs, rabbits, and cats and of 16 mm. Hg in dogs. He demonstrated a relationship between venous and intrarenal pressure similar to that found by Swann *et al.* (145), independence of interstitial pressure, and arterial pressure in the range of 40 to 140 mm. Hg and, as Winton (146) posited, a dependence of interstitial on ureteral pressure. Koza *et al.* (147) found that epinephrine causes equal percentile reductions in blood flow in normal, hypertensive, and sympathectomized hypertensive human subjects. They concluded that human, unlike canine, renal vasculature does not become epinephrine-hypersensitive after denervation. Further indirect evidence on the controls of human renal blood flow is that of Pfeiffer & Wolff (148), who found that lumbodorsal sympathectomy decreased the overresponsiveness of the renal vascular bed of hypertensive patients to vasoconstriction precipitated by personal discussion and confined the increased resistance to the afferent vessels. From this it seems that the efferents are under sympathetic control, while the afferents respond autonomously to increased pressure.

URINARY ACIDIFICATION

Maleic acid blocked formation of acid urine and caused the urine to become alkaline during acidosis, rich in sodium and bicarbonate, but not in chloride, with a resultant excess of measured cation over anion. Maleic acid was nephrotoxic in dogs infused with glucose [Berliner, Kennedy & Hilton (149)]. Pitts (150) has reviewed renal mechanisms of acid-base regulation, and suggested that ammonia formation is under adrenal control; he has restated concepts of ion-exchange of sodium for hydrogen and ammonium ions and noted the prediction that all such ionic exchanges may find a common mechanism. Binkley (151) accepted this challenge and outlined a concept in which the renal tubule was viewed as a column of self-regenerating ion exchange resin; enzymes concerned with hydrolysis of glutathione and glutamine represent resin in the analogy. Regenerative energy steps were provided by adenosinetriphosphate. He visualized a sodium pump, which can apply to sodium-potassium interactions and ion-exchanges of hydrogen and ammonia; since substances secreted in the proximal tubule, such as penicillin, the phthaleins, and PAH inhibit the enzyme, it may enter into tubular secretion also.

WATER

General properties of neonatal renal function include association of filtration rate and urine flow, lack of capacity to concentrate urine in response to pitressin, and inability to excrete or retain over- or under-loads of water and salt. In the rat, Falk (152) found that the response to a 5 per cent water load assumes adult character at 10 days; pitressin responses began at three days; adrenal cortical extracts enhanced water diuresis at any age. Dicker & Heller's newborn guinea pigs had virtually adult capacities for concentration

and dilution (153); these precocious newborn did show slow water diuresis and an association of glomerular filtration rate with urine flow.

Wolf (154) has constructed osmometric thirst diagrams for dog and man which relate this sensation to critical levels either of increased osmotic pressure of body fluids or cellular dehydration. However, Holmes & Gregersen (155) found large variations among dogs in water ingested in response to a standard salt infusion. Day-to-day responses in any one dog were consistent and dependent on salt load. Sucrose and sorbitol, which distributed only in extracellular fluid, were as effective as sodium chloride in eliciting thirst; glucose was much less effective. Paradoxically, sodium chloride deficit elicited by sucrose diuresis in dogs caused polydipsia and polyuria in spite of decreased extracellular osmolar concentration [Holmes & Cizek (156)]. Diuretic responses to water loads were not depressed, which reaction contrasts with Bristol's experience (157) in dogs or McCance's observations in man (157a). Tubular damage from sucrose might account for diuresis and maintenance of relatively large sodium outputs when the animals lived on sodium-poor diets. Cizek *et al.* (158) re-examined the problem by using peritoneal dialysis as a means of depletion. Their depleted animals, after recovery from a transitory depression and languor, began to drink more water than in control periods. The data dissociate this thirst from hyperosmolarity of body fluids. [Additional reports based upon studies in amphibia are the following: (159, 160, 161).]

The kangaroo rat, *Dipodomys* has little access to water in its natural environment. Since it is capable of very high U/P ratios of urea and electrolytes, Ames & van Dyke (162) postulated that it must have a very active ADH mechanism. In confirmation, they found up to 50 milliunits equivalent of ADH per milliliter in kangaroo rat urine and a maximum of only about six milliunits in urine of dog and cat under osmoreceptor stimulation. The ADS (antidiuretic substance) in *Dipodomys* urine corresponded well in its properties with pituitary ADH; pituitaries of these animals contained five to six times the ADH found in albino rats. O'Connor (163) has confirmed that hypertonic saline causes ADS to appear in the urine of normal, but not hypophysectomized dogs. Recovery of ADS activity in urine of dogs infused with posterior lobe extract was 7 to 15 per cent, and a steady output was obtained in about 20 min. From these data and the fact that output of ADS increased with increased concentrations of infused sodium chloride, he calculated maximum release rate of ADH as about one milliunit per minute. Release rates of 0.25 milliunit per minute maintained maximum water conservation. ADH had no specific effect on chloride output. Similarly, in man, pitressin (20 to 100 milliunit intravenously) never increased urinary outputs of sodium or chloride which often decreased during antidiuresis, [Chalmers, Lewis & Pawan (164)]. Brodsky & Rapoport (165) found no abnormality of urinary solute composition in clinical diabetes insipidus. They postulated that hypotonic urine formation is the result of distal tubular secretion of water and that pitressin acts by inhibiting secretion and promoting reab-

sorption. Like observations were made by Hare *et al.* (166) on normal dogs and during experimental diabetes insipidus (DI) under conditions of osmotic loading. The DI dogs differed from the normal only in that they excreted more water in amounts up to 15 per cent of filtration rate, which fraction seemed to depend on pitressin for its reabsorption. Deyrup (167) found that addition of one unit of pitressin to a rat kidney slice increased oxygen consumption, but the amount seems excessive and the effect artefactual. Birnie *et al.* (168) found ADS with some properties of ADH in normal rat serum but not in hypophysectomized rats. Serum ADS accumulation after adrenalectomy is prevented by saline, DCA, or cortical extracts, which may stimulate ADH-destroying mechanisms. Overtreatment with cortical hormone does not reduce the normal serum ADS concentration. Dicker & Ginsburg (169) could not demonstrate ADS in fresh rat plasma and viewed the serum ADS as a product of clotting other than serotonin. That ADH is sometimes demonstrable in blood is apparent from detection of as much as 50 milliunits per 100 ml. in jugular blood of dogs during osmoreceptor stimulation [Ames, Moore & Van Dyke (170)]; the substance or substances thus demonstrated were not physically homogenous.

Pitressin seemed to have two active principles since sodium thioglycollate destroyed its ADS activity in dogs, but not in rats [Ralli *et al.* (171)], until Ames & van Dyke (172) found that thioglycollate is itself antidiuretic in rats. Extrahypophyseal formation of an ADS occurs *in vitro* [Croxatto, Rojas & Barnafi (173)] when renin substrate fractions digested with pepsin are redigested. This (presumed) peptide is of interest because of the chemical analogies between angiotonin (hypertensin), pepsitensin, pitressin, and oxytocin. However, angiotonin [Hughes-Jones *et al.* (174)] is itself diuretic rather than antidiuretic. Whole body irradiation of rats caused spontaneous diuresis and increased diuretic responses to water loads with depression of serum ADS content [Edelmann & Eversole (175)]. Spray irradiation of dogs had no evident effect on any compartment of body fluid [Soberman *et al.* (176)]. Like pitocin [Page (177)], pitressin is quickly inactivated by the blood of women in the latter half of pregnancy [Dieckmann *et al.* (178)].

Cates & Harrod (179) injected nicotine as a test stimulus in suspected diabetes insipidus. A patient, who had lost her symptoms and who failed to respond to the test of Hickey & Hare (180), failed to respond to nicotine; this suggested that there may be latent, unrecognized means of controlling water loss. Chalmers & Lewis (181) found that emotional stress and injections of hypertonic saline, acetylcholine, or nicotine, all elicited release of ADH; smoking up to three cigarettes was also an adequate stimulus. On this basis, they [Lewis & Chalmers (182)] tested 11 cases of clinical diabetes insipidus. Evidence of residual ADH function persisted in four. Ability of hypophysectomized dogs to excrete water loads is impaired. This may be due to lack of growth hormone which, in a dose of 1 mg. per kg. body weight restored water diuresis and increased water turnover to levels found in experimental diabetes insipidus dogs [de Bodo *et al.* (183)] although their prepara-

tions did not fully restore RPF or GFR. White, Heinbecker & Rolf (184) found that preparations of growth hormone vary in their ability to affect these functions and T_{PAH} . Some that are fully effective in hypophysectomized dogs are not effective in normal dogs. They adhere to the view that renotropic effects of pituitary extracts are substantially attributable to their content in growth hormone. In rats the decrease of renal weight that follows hypophysectomy is not attributable to weight loss, hypoalimentation, or lack of urea output; however, defective thyroid function is an important factor [Braun-Menendez (185)]. Similarly, some part of the renotropic activity of growth hormone preparations can be attributed to contamination with thyrotrophin (184).

Clinical studies correlate with experimental in that most patients with chromophobe adenoma and resultant hypopituitarism show low rates of glomerular filtration and renal plasma flow (C_{In} and C_{D}) and slowing of water diuresis [Pickford & Watt (186)]. In their experience, as in that of Luft & Sjögren (187), renal clearances in acromegaly were either normal or low, which indicates that growth hormone has no substantial renotropic effects in man. Luft & Sjögren (187) found that administration of DCA and sodium chloride increased GFR in pituitary deficiencies without affecting RBF; combined therapy with DCA and thyroxine restored both functions nearly to normal. A similar progression was demonstrated in a patient with hypertension [Luft & Sjögren (188)].

Jørgensen (189) suggested that adrenal cortical mechanisms, even in frogs, influence water and electrolyte metabolism. Decreases in filtration rate, urine flow, and water diuresis occurred in adrenalectomized rats [Boss, Birnie & Gaunt (190)]; large doses of DCA or adrenal cortical extract restored urine flow without fully restoring filtration rate, apparently by suppressing tubular reabsorption of water. Such rats have a normal ability to excrete a load of Ringer's solution [Kellogg *et al.* (191)]. Physiological participation of the adrenal cortex in full water diuresis is suggested by the adrenal cortical ascorbic acid depletion found in rats given large water loads by Nagareda & Gaunt (192), who advanced the concept that maximum water diuresis results from the convergent effects of inhibition of ADH secretion and adrenal cortical stimulation. Water metabolism is also affected by adrenal medullary hormones. Horres, Eversole & Rock (193) found that pure *l*-epinephrine did not stimulate diuresis in rats, that norepinephrine did, and that the diuretic action of epinephrine is attributable to its content of norepinephrine. Dibenamine (N,N-dibenzyl- β -chloroethylamine) partially blocked the action of norepinephrine and completely that of epinephrine. Cook, Hambourger & Green (194) found that epinephrine and norepinephrine both decreased water and electrolyte clearances in dogs and that Dibenamine in doses that prevented any blood pressure rise did not block the renal effects of norepinephrine. A sodium-retaining effect of epinephrine has also been shown in dogs by Blake (195). In human beings, norepinephrine decreased C_{D} , increased filtration fraction (FF) and caused a questionably sig-

nificant restriction of urine flow [Barnett *et al.* (196)]. Baez, Mazur & Shorr (197) and Shorr *et al.* (198) suggested that ferritin [vasodepressor material (VDM)] antidiuresis is due to stimulation of ADH secretion; it was absent after pituitary stalk resection. VDM activity in plasma of oliguric patients led to the suggestion that this mechanism is concerned in a variety of conditions in which water is retained, such as hepatic cirrhosis and congestive heart failure in which, however, the consensus is that sodium and not water is primarily affected. Sodium cyanate elicited water and electrolyte diuresis and depressed GFR in rats [Dicker (199)]; the diuresis was unchanged by pitressin. Urethane and colchicine [Dicker (200)], which like cyanate, [Dicker (199)] are antimitotic, also elicit diuresis; urethane diuresis is associated with increases in sodium and chloride outputs and GFR; colchicine did not alter electrolyte output, but did depress GFR. The common renal aspect of antimitotic activity is facilitation of water output.

Clinical tests of effects of sedatives and hypnotics on diuresis in pregnancy have been summarized by Brown, Hodges, & Broadberry (201). Morphine antidiuresis is associated with decreased RBF; Avertin (tribromoethanol solution) and Amytal (5-ethyl-5-isoamylbarbituric acid; amobarbital) did not have this effect. Small doses of morphine depressed RBF, filtration rate, and urine flow, but did not alter arterial pressure in dogs; larger doses of morphine depressed arterial pressure and suppressed urine formation [Handley & Moyer (202)]. Dromoran (3-hydroxy-N-methyl morphinan hydrobromide), which is more potent as an analgesic than morphine is in man, was equally antidiuretic in dogs [Siegel *et al.* (203)]; neither one of the drugs caused chloruresis. Handley & Keller (204) considered that morphine slows urine flow by (a) decreasing the number of active nephrons and (b) stimulating release of ADH. Strauss, Rosenbaum & Nelson (205) found in man that alcohol causes a diuresis which results in hypertonicity of body fluids; it is inhibited by pitressin or ingestion of salt. Alcohol seems to act by depressing responsiveness of the central ADH mechanisms. The substituted 3-hydroxycinchonic acids also act on this mechanism, but in an opposite sense [Maren & Bodian (206)]; nicotine and 3-hydroxy-2-phenylcinchoninic acid were not antidiuretic in subtotally neurohypophysectomized rats, although sometimes effective in clinical diabetes insipidus.

CLINICAL DISEASE

Illness uncovers many aspects of renal physiology. Reviews by Darrow & Pratt (207) on fluid and electrolyte therapy in general and by Hoffman (208) on potassium are noteworthy. The tendency of some to overrestrict postoperative replacement with sodium chloride may be lessened by Ariel & Miller's demonstration (209) of the concurrence of hyponatremia with depression of RPF, GFR, and Tm_{PAH} , and Bristol's observation (157) that hyponatremia predisposes to water intoxication. Randall *et al.* (210) have shown the unreliability of urine chloride as a guide to postoperative replace-

ment therapy. Sirota & Kroop (211) found hyponatremia and expanded inulin space in acute renal insufficiency; they postulated a shift of water from cells and of sodium into them as part of the uremic state. The reverse obtains in heart failure, in which Iseri, Boyle & Myers (107) estimated that water passed into cells and sodium and potassium, which had been in part osmotically inactive, shift out. Eunatremia and eukalemia in the face of urea, creatinine and phosphate retention in chronic renal disease are accomplished by the concurrence of decreased reabsorption with decreased filtration [Platt (212)]. Untoward tubular secretion of potassium may explain the hypokalemia Kolff (213) found in 9 of 16 uremics; however, serum potassium usually begins to increase as GFR falls below half normal [Farber *et al.* (214)]. Brown *et al.* (215) have pointed out that potassium clearance may be very low in cardiac failure in spite of adequate urine volume. Rapoport *et al.* (216) have drawn attention to the probability of proximal tubular inadequacy of sodium and chloride reabsorptions in tuberculous meningitis. Hyponatremia attributed to depletion of cellular electrolytes occurs in pulmonary tuberculosis [Sims *et al.* (217)].

The sequence elicited by infused concentrated albumin is interpreted by Luetscher *et al.* (218) as follows: (a) increased plasma colloid osmotic pressure, (b) resultant plasma dilution, (c) increase in GFR with (d) water diuresis, and (e) resultant shift of sodium into plasma; tubular sodium rejection may be induced so that diuresis continues and serum protein rises. An alternative suggestion involves the increased secretion of ADH and possibly of adrenal sodium-retaining hormones. Epstein *et al.* (219) have confirmed, by relatively direct means, increased sodium reabsorption by patients with hepatic cirrhosis in the stage of edema formation; they could not correlate this with the degree or direction of hepatic function. This abnormality was attributed by Eisenmenger *et al.* (220) to adrenal desoxycorticosterone-like hormones. Recovery was presaged by increased urinary sodium. Two non-edematous cirrhotics responded normally to sodium loads [Goodyer *et al.* (221)], but patients in the edematous phase retained both sodium and potassium. In cirrhosis [Jones *et al.* (222)] as in cardiac failure [Baldwin, Sirota & Villareal (223)] GFR increases nocturnally; in normal people as in cirrhotics, this is associated with an increase in U/P inulin; in congestive failure there results an increase in urine volume and sodium output. Patients in cardiac failure showed an inverse relationship between filtration fraction and urine flow [Brod & Fejfar (224)]. Nocturnal increases in RPF and GFR did not occur in the severely disabled. Fejfar & Brod (225) found chloride output and urine flow more closely correlated with each other than with GFR or chloride load and suggested the chloride retention is in part a result of oliguria. Decreased RPF in congestive failure is not a function of an absolute decrease in cardiac output [Fishman *et al.* (226), Davies & Kilpatrick (227)], since RBF and renal fraction are depressed in the high output failure of cor pulmonale. Like those of Grossman *et al.* (228), their (226, 227) patients showed normal E_{PRAH} during congestive failure. A parallelism existed between sodium out-

put and RBF (226) but the association of sodium output with GFR and sodium load was sufficiently irregular (227) to suggest participation of active tubular sodium retention. Tm_{PAH} was within normal limits in one series (225) and both Tm_{PAH} and Tm_G in another (227). Grossman *et al.* (228) reaffirmed the concept of glomerulo-tubular imbalance as the determinant of sodium retention. Dissociation of GFR, sodium output and cardiac output and a relation of sodium retention to shifts in distribution of body fluids was suggested by Greve *et al.* (229) from a study of the effects of digitoxin in normal men. Anoxia is not a factor in the renal ischemia of congestive failure. Relief of anoxia depresses RBF and vice versa (226). Perhaps the most that can be said with certainty is that the evidence points well away from the participation of preglomerular renal shunts.

Decreased RPF in senescence has been confirmed [Olbrich *et al.* (230)]. McDonald *et al.* (231) examined effects of pyrogen hyperemia in the aged who show the presence of afferent and efferent renal vasoconstriction; like patients with essential hypertension [Taylor *et al.* (232)], the aged had an irreversible residual resistance, presumably due to afferent arteriosclerosis. Hypertensives with low RBF respond unsatisfactorily to lumbodorsal sympathectomy; FF was not an index of response (233, 234). Correlation of levels of GFR (from C_M) and RPF (from C_{PAH}) with histological change was demonstrated (233, 234, 235).

Additional pertinent clinical studies include: differentiation of Types I and II glomerulo-nephritis (236); methionine metabolism in nephrotic children (237); cortisone in treatment of the nephrotic syndrome (238); urinary sediment and protein in systemic lupus erythematosus (239); nephrocalcinosis and renal damage (240, 241). Functional changes in renal diseases have been admirably reviewed by Bradley *et al.* (242).

EXPERIMENTAL DISEASE

Hypertension.—Swann & Prine (243) attributed perinephritic hypertension to increased intrarenal pressure; the same might explain the transitory hypertension deFelice (244) found in rabbits with ligated renal lymphatics. Divry (245) showed that release of pressor substance(s) from kidney could be elicited by decreased pressure resulting from arterial compression, but not by hypoxia; pressor releases occurred without change in renal oxygen consumption. Olsen & Schroeder (246) found decreased oxygen tension and pH in renal cortex of dogs with chronic renal hypertension and concluded that cortical anoxia may be a factor in the acute and chronic effects of arterial compressions. That the basic disturbance may be still more subtle was suggested by the association of experimental renal hypertension with clumping of tetrazolium-reducing compounds (dehydrogenases, diaphorase) in and around renal cells [Zweifach, Black & Shorr (247)].

Participation of the renal pressor system in renal hypertension is still in question. Thus, hypertension persisted in renal hypertensive rabbits made tachyphylactic to renin [Flasher & Drury (248)] and after hepatectomy in

absence of renin substrate [Drury *et al.* (249)]. However, Davis & Tanturi (250) attributed decreased arterial pressure in renal hypertensive dogs to depressed substrate formation consequent on experimentally decreased hepatic blood flow and fatty infiltration. Govaerts, Verniory & Lebrun (251) considered renin an unlikely pathogenic agent in renal hypertension because renal hypertensive dogs were neither hyperresponsive to it nor showed increased renal venous renin concentrations. A cogent, albeit indirect, argument in favor of the renin hypothesis could be based on preventive and therapeutic effects of antirenin in renal hypertensive dogs [Bird *et al.* (252); Moore *et al.* (253)]. Repeated injections of rabbits with renin did not lead to lasting hypertension [Strehler & Suter (254)], although they did cause cachexia in rats [Masson, Corcoran & Page (255)]. Intravenous infusion of small amounts of renin over a fortnight increased arterial pressure during this time [Blacket *et al.* (256)]; the calculated amounts of renin necessary to sustain renal hypertension in rabbits would yield 0.002 unit per milliliter of renal venous blood which would be undetectable by present methods. Skeggs, Kahn & Shumway (257) seem to have shown that angiotonin occurs in dialysates of blood from normal and hypertensive dogs; more was present in recent renal hypertension. Moeller & Kopperman (258) found that patients with acute and chronic hypertensive glomerulonephritis and malignant nephrosclerosis showed hyperresponsiveness to injected human renin; patients with essential hypertension did not. Some of the hypersensitive nephritics showed a subsequent fall of resting arterial pressure attributed by Moeller & Kopperman to desensitization. That renal nerves participate in renin formation was indicated by Fasciolo & Taquini (259), although subtotal renal ischemia was also a stimulus [Taquini (260)]. Uncertainties about renin are based in part on the crudity of preparations in current use. A 90 per cent pure renin described by Haas, Lamfrom & Goldblatt (261) may resolve these.

Renal-adrenal participation in the maintenance of renal hypertension in rats has been proposed [Masson, Corcoran & Page (262)]. The concept is based in part on the effect of renin and renal hypertension on the zona glomerulosa [Deane & Masson (78)] and is supported by Braun-Menendez's observation (263) that electrolyte distribution in renal hypertensive rats is similar to that elicited by DCA treatment. Fasciolo (264), who reviewed the present status of renin, also considered its connection with electrolyte metabolism. Tosteson *et al.* (265) found adrenal participation in this particular aspect of renal hypertension doubtful, since avoidance of sodium by renal hypertensive rats on self-selection diets is independent of the presence of the adrenal. A linkage of renal and DCA hypertension was indicated by Friedman, Friedman & Nakashima (266), who attributed to continuing renal metabolic disorder the persistence of hypertension in rats after DCA treatment had been stopped. They found in contrast to our experience that cortisone prevents DCA hypertension (267); we agree that it adds to the severity of renal lesions. Braun-Menendez & Prado (268) confirmed that sodium chloride intake is necessary to DCA hypertension and suggested that

electrolyte distribution, as well as renal lesions, participated in increasing pressure. The merely supportive role of the steroid as such is indicated by the hypertension which appeared in adrenalectomized, nephritic rats fed sodium chloride [Knowlton *et al.* (269)].

Schroeder's review of pathogenesis of hypertension (270) combined clinical and experimental aspects into a pattern of multiple causation similar to that proposed by Page (271). Schroeder & Olsen (272, 273) presented a preliminary characterization of pherentasin; it is a pressor amine found more commonly in hypertensive than in normal blood and most commonly in patients with renal hypertension. Renal amine metabolism may be a causal factor in renal hypertension. This view obtains some support from the varying responsiveness of renal hypertensive rats to different pressor amines [Olsen *et al.* (274)] and from the changes of oxidation rates of amino acids and amines in kidneys of hypertensive rats [Olsen (275)]. An unidentified pressor substance of remarkably prolonged action was found in normal human urine by Handler & Bernheim (276).

Somatotrophic hormone (growth hormone) elicits hypertensive disease in rats [Selye (277)] and sensitizes to toxic effects of DCA (Selye (278)); cortisone protects against some of its effects. Responsiveness of the rat to hypertensive disease is indicated by the addition of thyroxine to the list of agents which cause it [Selye (279)]. Danford *et al.* (280), found that sodium restriction reduced arterial pressure and increased survival in renal hypertensive rats. Handler & Bernheim (281, 282) found that postcholine-deficiency hypertensive rats, like renal hypertensives in their hands, respond to both protein and salt restriction and to renal decapsulation; also after decapsulation, hypertension is restored by ACTH (283). Handler & Bernheim suggest that the hypotensive effect of protein restriction depends on decreased formation of ACTH and relates it to choline metabolism (284). In dogs, cortisone and ACTH have only negligible effects on renal hypertension [Grollman & Konnerth (285)].

Abscess in dogs (a form of pyrogen disorder) decreased peripheral resistance and increased RBF and renal fraction with unchanged cardiac output in normal, "spontaneous" and renal hypertensive dogs; but Stamler *et al.* (286) found that superimposition of pentobarbital anesthesia further reduced peripheral resistance and, by evoking compensatory mechanisms, decreased renal fraction and increased cardiac output. Pyrogen-induced renal hyperemia was suppressed by dihydroergocornine, apparently by central action [Talos & Moe (287)]. Cinchona alkaloids elicited renal hyperemia and decreased arterial pressure in normal and neurogenic hypertensive dogs; they were ineffective in either regard in dogs with renal hypertension [Greene & Hiatt (288)]. A disparity was also found with veratrine which decreased both arterial pressure and RBF in renal hypertension; it increased RBF and decreased pressure in normal and neurogenic hypertensive dogs [Nungesser & Hiatt (289)].

Nephritis.—Nephrotoxic rabbit sera in rats provoked glomerular lesions,

azotemia and lipemia which began within the hour, and hypoproteinemia at 8 hr. [Heymann & Hackel (290)]. Pressman *et al.* (291) have confirmed localization of antikidney serum on mouse glomeruli by tagging antibody with S^{35} . Greenspon & Krakower (292) have localized antigenicity of kidney to the glomerular basement membrane. That there is some lack of organ specificity was shown by the glomerulonephritis caused by rabbit antidog-placenta serum in dogs [Seegal *et al.* (293)]. Hypertensive vascular disease occurred in a large proportion of rats placed in parabiosis [Hall & Hall (294)], probably also as an immunologic response.

Long-continued, small daily injections of horse serum caused glomerulonephritis in rabbits without arteritis or valvulitis [McLean *et al.* (295)]; larger doses of horse serum or bovine γ -globulin caused glomerulonephritis with arteritis and valvulitis; a mixture of the proteins with killed streptococci elicited bilateral renal cortical necrosis; a mixture of Freund's adjuvant with protein or protein plus cocci suppressed the effects of both [More & Kobernick (296)]. Lange *et al.* (297) found serum complement titers in clinical glomerulonephritis which varied inversely with activity of disease. This finding suggests that the disease is due to an antigen-antibody reaction. An experimental basis for the clinical custom of imposing rest in bed in acute nephritis can be found in the deterioration caused by forced work in acute nephrotoxic nephritis in rabbits [Steinman & Kaufman (298)]. Cortisone protected rabbits against horse serum arteritis and the Arthus reaction but did not prevent glomerulonephritis [Seifter *et al.* (299)], nor did either cortisone or ACTH protect against nephrotoxic serum glomerulonephritis in rats [Hackel *et al.* (300)]. Indeed, it may have facilitated renal cortical necrosis in rabbits given bacterial toxins [Thomas & Good (301)]. Clinically it did not ameliorate the nephropathy of systemic (disseminated) lupus erythematosus, although remission of extrarenal lesions occurred [Heller *et al.* (302)].

Hemoglobinuric nephrosis.—Prolonged faradization of rats caused renal hemosiderosis in which the pigment was distributed (a) by athrocytosis in cells of the proximal tubule, (b) perivascularly in cortical areas of tubular damage, and (c) in masses in medullary collecting tubules [Hirsch (303)]. Long-continued stimulation of the cerebral cortex in cats was found by Hoff & Kell (304) to elicit partial and, when combined with oligemic shock, outspoken lesions of "lower nephron nephrosis" with uremia; effects on the kidney were prevented by cervical cord section and by Dibenamine. Cort (305) found in rats that a combination of limb crush and tourniquet application caused anuria (without renal lesions) which lasted over 48 hr. and at 24 hr. was reversed by paravertebral ganglionic (T-5 to L-1) application of procaine. Thus, in the wake of Trueta (138), neurogenic mechanisms have been emphasized; however, Clark, Barker & Crosley (306) found no evidence of shunting and normal renal arteriovenous oxygen and carbon dioxide difference in a patient with hemoglobinuric nephrosis.

The wide distribution of causes of the "lower nephron syndrome" is emphasized by the addition of phosphorus poisoning in man [Diaz-Rivera

et al. (307)]. However, the lesion is not readily, if at all, reproducible in dogs. Thus, severe hemolysis due to ultrasonic vibration rarely resulted in renal failure in this species [Olsen & Necheles (308)], although, combined with surgical shock, mortality may be severe [Scruggs, Olsen & Necheles (309)]. Thus also, Parsonnet, Fishler & Thalheimer (310) found that shock plus hemoglobinuria with or without red cell stroma did not produce hemoglobinuric nephrosis in dogs. Studies of severely wounded men has led Mallory *et al.* (311) to the view that they excrete hemoglobin or myoglobin at low plasma levels and that some show myoglobinuria without demonstrable muscle lesions. Lippman's observations on facilitation of hemoglobin excretion by renin and other proteins may bear on their hypothesis (18). Muirhead (312) has described a hemorrhagic diathesis in the wake of hemolytic transfusion reactions; he emphasized conservative management of uremia.

Uremia.—Castro-Mendoza, Jiménez Díaz & Linazasoro (318) attributed to a renal extract a control of capillary permeability since it prevented decreased plasma volume and increased serum protein concentration in nephrectomized dogs. Baker (319), who used an ingenious means of eliciting controlled uremia, has shown that serum albumin in uremic dogs as in uremic patients, has a decreased capacity for binding phenol red. The centrally distributed pulmonary alveolar thickening and inflammation of uremia was studied by Bass & Singer (320). The effect of amino acid and protein feeding on survival of rats with ligated ureters was examined by Lindberg & Freeman (321); they found saline, isoleucine, and leucine had little effect; glutamic acid and histidine were very toxic; casein hydrolyzates and amino acid mixtures were more toxic than enzymatic plasma digests.

Modifications of the artificial kidney [Rosenak & Saltzman (322); Low-ley & Kirwin (323)] continued to be described. Life-saving effects of vivo-dialysis have been proven in rabbits with mercuric chloride poisoning by Norbiit (324). Methods of treating uremia have been reviewed by Kolff (325), whose emphasis is on conservative dietary management; intestinal perfusion with sodium sulfate [Maluf (326)], irrigation of intestinal loops [Sloan (327)], cross-transfusion [Bierman *et al.* (328)], and homotransplantation of the kidney [Lawler *et al.* (329)] have been reported. This last is ineffective and the next to last dangerous. Perhaps the most practical means of emergency treatment of uremia is intermittent peritoneal lavage [Grollman, Turner & McLean (330)]. Nephrectomized dogs have thus survived up to 70 days, but they developed hypertension and medial necrosis of arteries and myocardium [Grollman, Turner, Levitch & Hill (331); Muirhead, Grollman & Vanatta (332)] such as was observed in an anuric man by Muirhead & Grollman (333). Thus, the prospect of indefinite arenal survival may have to be re-examined in terms of an as yet incompletely defined renal incretory function.

METHODS AND PROCEDURES

Olbrich *et al.* (334) propose simplified procedures for clinical determination of renal clearances (inulin and diodrast) that tended to minimize the

errors of simple slope analysis (335, 336). In the formulation of Houck (337), the possibility of nonexcretory renal utilization of mannitol is overlooked. Camara *et al.* (338) advocated the 24-hr. endogenous creatinine clearance after 48 hr. subsistence on a low meat diet as a clinical measure of renal function. Hare & Hare (339) proposed analysis of endogenous creatinine after elution from Lloyd's reagent. Sodium ferrocyanide was used for measurement of renal clearance and extracellular fluid in infants [Calcagno, Husson & Rubin (340)]; the data indicate some renal tubular reabsorption of ferrocyanide [mean $C_{Fe(CN)_6}/C_{In}$ was 0.85].

Moses, Emery & Schlegel (341) reported the separation from Thioflavine S of a fraction (Vaso-flavine) better adapted to visualization of blood vessels. Robinson (342) suggested demonstration of carbonic anhydrase activity in urine as a simple test for detection of intravascular hemolysis.

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EXCITATION, CONDUCTION, AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM¹

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The ultimate aim of neurophysiological research is the solution of three fundamental problems. In brief, these problems are: (a) what is excitation and the process which brings it about; (b) what is the mechanism of inhibition; and (c) what processes are involved in conditioning and the preservation of the effects of a stimulus experience for long periods of time?

The object of this review is to describe the recent progress which has been made toward the solution of these three basic functional problems of neurophysiology.

EXCITATION

The properties of the membrane.—The interest in general biophysical problems related to excitation is still centered on the relative role exerted by ionic movements and by metabolic factors upon the electrical properties of the membranes. It is generally agreed that the classical Bernstein theory does not fully account for all experimental findings, but the extent to which this theory should be modified is still a matter of discussion.

One of the major reasons for the disagreement seems to be the differences in interpretation of the influence of the epineurium in determining the distribution of current at the surface of nerve trunks and the speed of exchange of chemicals and of ions between external fluids and nerve fibers. Current distribution in and ionic influences upon nerve trunks surrounded by connective tissue are clearly inconsistent with the core cable theory (162, 189). This should therefore be rejected unless reasons can be produced for believing that the divergencies are due to the sheath. The problem of the epineurium was originally mentioned by Bishop and co-workers (27). The finding by Feng & Gerard (92), and by Rashbass & Rushton (189) that removal of the epineurium drastically changes the mentioned properties of nerve trunks has been extensively confirmed by Feng & Liu (93) and Crescitelli (63) and, indeed, is not challenged as an experimental result. Lorente de Nó (161), however, maintains that the acceleration of the action of chemicals and ions on nerve fibers, which takes place following the removal of the sheath, is due to damage to the fibers which results in unphysiological sensitization to these agents. The main argument in support of this view is the finding that the first detectable action of environmental fluids on a nerve trunk is rapid, while the total action on all fibers is extremely slow (159, 161). Moreover,

¹ The survey of the literature pertaining to this review was concluded June 30, 1951.

"the past history of the fibers" (161, p. 220), and allegedly not of the epineurium [see (132, 189) for criticism] determines the rate of action of ions on nerve excitability. As evidence of the fact that the epineurium is not polarizable, the finding (162) that the slow component of the electrotonus is altered by agents which are assumed to act specifically upon the nerve fibers [anesthesia, anoxia, temperature, frequency of excitation; see, however (189)] is quoted. These arguments, if they have been properly understood, are open to alternative interpretation. In particular, the claim that removal of the sheath alters basic properties of the fiber is unconvincing in view of the fact that all alterations can be ascribed merely to removal of connective tissue and also because of the finding that medullated nerves deprived of the epineurium behave much like the structures in which epineurium is naturally not present.

Permeability (63) and electrical properties (38) have been measured first in nerve trunks with intact sheath, then after removal of the sheath, and finally after its restoration to the fibers. The latter procedure reproduces the original properties, indicating that if the fibers are damaged by the removal of the sheath, this damage is reversed when the epineurium is reapplied; it is more probable that this is not a reversible damage, but that the sheath itself is responsible for the changes. O. H. Schmitt, quoted by Schoepfle & Susman (202), has found appreciable capacity in the isolated, intact epineurium of frogs.

Granting that the results on polarization, permeability, and excitability of nerve trunks which are fully contradictory to the core cable theory are vitiated by the presence of connective tissue around the nerve, no reason exists to reject the theory *in toto*, and it can be considered to what extent it should be modified. An hypothesis that gives satisfactory explanation of the results which could not be included in the classical theory has been produced by Hodgkin & Katz (128) and has already been reviewed (53, 111). In recent articles, this hypothesis is restated, explained, and discussed (121, 122).

A number of important experimental results show good agreement with the proposed hypothesis. Huxley & Stämpfli (133, 136) have measured the resting and action potential of single medullated fibers of frog's nerves by means of an ingenious method which does not require internal electrodes. After corrections made to compensate for the calculated junctional potentials, they find average values of 71 mv. for the resting potential and 116 mv. for the action potential, as compared with ± 55 mv. found for both by Lorente de N6 (162). Similar measurements have been made by Svætichin with internal microelectrodes (207). The specific resistance of the axoplasm is found to be slightly higher than that of Ringer fluid and consistent with the accepted view that ordinary ionic movements account for the current flow in axons. Hodgkin & Keynes' results (129) showing that internal K^+ is in free ionic form indicate that K^+ will contribute to this current flow. In agreement with previous findings in nonmedullated axons (120, 128) and in

muscles (186), lowering of external K^+ concentration increases and raising K^+ concentration decreases both resting potential and the overshoot. Lowering external Na^+ concentration slightly raises the resting potential and markedly decreases the overshoot. The maximal rate of rise of the action potential is found to be roughly proportional to the external Na^+ concentration [see Hodgkin & Katz (128)]. The quantitative relation between K^+ concentration and the value of the resting potential shows, however, that this cannot be exclusively due to selective permeability to K^+ . The deviation from the theoretical slope can be explained, assuming a minor degree of permeability to Na^+ and Cl^- . Also it is likely that a metabolic process involved in the maintenance of the resting potential in normal nerves does not take place in experimental conditions involving excised single fibers [Huxley & Stämpfli (137)].

The use of radioactive materials allows a direct study of the movement of ions across the membrane in the resting state and during activity. This method has demonstrated (144, 145, 146) that K^+ is exchanged freely between excised nerve fibers and outside fluid (60, 146), but a steady net loss from the fibers takes place. Since this cannot be true in normal intact tissues, it must be assumed that a physiological mechanism responsible for K^+ reabsorption is not operating in excised nerves (127, 137). During periods of repetitive excitation the rate of K^+ exchange is increased. The leakage is raised to 10 times and the intake to 1.7 times the resting values by stimulation at 50 stimuli per sec. The net leakage of K^+ during activity can be calculated to be about 2.4×10^{-12} moles per sq. cm. per impulse. The rate of entry of Na^+ during activity is calculated to be approximately of the same order (144, 146). These findings indicate that the quantity of K^+ leakage in activity is more than sufficient for recharging the membrane capacity, but they do not support directly Hodgkin & Katz's hypothesis (128), since they cannot prove that the K^+ leakage corresponds to the descending phase of the spike. This required temporal relation is strongly supported by recent experiments summarized by Hodgkin & Huxley (127). Results obtained by Rothenberg (194) are in fundamental agreement with the quoted ones. Values of Na^+ entry during activity, consistent with these, are found also by Nachmansohn (181) who speculates that the acetylcholine metabolism is an essential link in the mechanisms responsible for the membrane changes during activity. Results confirming directly the idea that the action potential exceeds the resting potential have been obtained on elements of cardiac muscles by Weidman *et al.* (71, 230). Extending the method of internal electrodes introduced by Ling & Gerard (155), resting and action potentials of cardiac muscle have been measured directly. The respective values are 90 mv. and 121 mv. in dog's "false tendons" and 94 mv. and 135 mv. in the Purkinje fibers of the kid. The action potential rises to a summit within 0.5 msec; repolarization is rapid in the initial phases, but its further development is slow, involving hundreds of milliseconds. From the level of maximal polarization, the membrane depolarizes slowly during diastole until a level

is reached at which the rapid upstroke of the action potential takes place. The conduction velocity of the action potential is in the range of 2.0 m. per sec. The rapid overshoot has been shown to be the most labile component of the action potential, since it is not present after the fiber has sustained damage or undergone deterioration after being pierced by too large an electrode (99). Decrease of external Na^+ has little effect on the resting potential but causes a large decrease in the action potential, which follows approximately a slope of 61.5 mv. for the tenfold change of external concentration (71).

The electrical resistance of the membrane was found to decrease profoundly during the phase of overshoot, while during the plateau its value is similar to the one found in diastole. Cathodal pulses applied during diastole evoked graded activity followed by signs of postcathodal depression, while enhancement followed the break of anodal pulses similarly applied. Anodal pulses delivered during the rapid upstroke of the action potential, if strong enough, could give rise to a propagated wave of repolarization. The resistance changes during, and the effect of external Na^+ on, the rising phase of the action potential can be considered a direct confirmation of the suggestion that this is brought about by a sudden increase in Na^+ permeability. The other results are at least consistent with it, and possible processes underlying the various phases of the action potential are discussed with relation to this hypothesis (230). In cold-blooded animals, however, the impedance rises during activity (192). The action potential of frog's heart fibers recorded through an internal electrode is roughly similar to the one found in mammals, but the times involved in both depolarization and repolarization are greater. In the experiments by Woodbury and co-workers (232), the rising phase of the action potential was possibly distorted by the recording instrument, but no rapid phase corresponding to the initial spike, which is related in mammals to resistance drop, seems to be present. The average resting potential has been found to be 64 mv. and the action potential 77 mv. That the average values might be lower than the real ones is indicated by the finding that higher values are recorded when the electrode tip is very thin.

The technical approach to the problem of measurement of the physical properties of the membrane is discussed briefly by Cole (58) in relation to the squid axon. Katz (139) has demonstrated that the membrane capacity of muscle fibers is about five times larger than that of nerves, and he discusses the possible significance of this finding in relation to conduction velocity and time constant of excitation of the same elements. Despite all these supporting results, the membrane theory is completely and emphatically rejected by Barnes (14, 15, 16), who considers it a major obstacle to progress in neurophysiology. An interesting attempt to relate all bioelectric phenomena to respiratory catalysis is made by Arvanitaki & Chalazonitis (11).

Tobias (221) finds a potential amounting to 20 to 25 mv. between a crushed and a noncrushed portion of a frog's muscle and to 38 mv. between the inside and the outside of a single fiber after depleting most of the inside K^+ by soaking the muscle for a day or more in running distilled water. The

author recognizes that, while the results may be interesting indications that a considerable electromotive force can be produced by grossly abnormal tissues, they do not give any clear information on the nature of the electromotive force of the normal membrane.

A group of papers by Fleckenstein and co-workers (94, 95, 96) indicates that the actions of certain drugs on muscles and nerves can be explained by their effect on the polarization of muscle fibers. Drugs with antagonistic effects on polarization display an equally antagonistic mechanical effect. In particular, anesthetic substances which prevent depolarization or which repolarize the membrane have been found also to protect from conduction block induced by depolarizing agents or even to restore conduction after the block has occurred [see Lorente de N6 (162)]. A more exacting study by Posternak *et al.* (188) shows, however, that some narcotic drugs act on nerves through a mechanism other than by changing the polarization of the fibers because the narcotic effect of different alcohols is not simply related to the changes they induce in the resting potential.

The results thus far quoted do give satisfactory experimental support to the assumption that selective K^+ permeability plus some amount of permeability to Na^+ and Cl^- account for the resting potential. On the other hand, it is clear that metabolic processes are also essential for maintaining the resting potential over long periods of time. Metabolic activity is necessary as a source of energy for re-establishment of the ionic balance altered progressively during rest and rapidly during activity, but little is known of the possible mechanisms involved. A conceptual model which has often been suggested is that ionic actions should be regarded "as a storage battery in parallel with a metabolic source of energy" (122). The justification for emphasizing the ionic mechanisms instead of the metabolic ones is offered by the fact that the former seem at present to be more amenable to experimental test, a fact, of course, which does not decrease the importance of experimental contributions resulting from the study of metabolic factors. The experimental confirmation of the hypothesis that rapid entry of Na^+ accounts for the rising and rapid K^+ exit for the decaying phases of the action potential is as satisfactory as could be expected at the present time. It is not clear, however, that this mechanism applies universally (219, 220), and in any case it has been shown that even when the Na^+ action is involved in activity under normal conditions, the role of this ion apparently can be assumed by other ions (90, 160).

Systematic studies of metabolic requirements of excitation have been undertaken by the Biophysics unit at Baltimore (40, 57, 59), and it is hoped that full publication of the results soon will be made available. Also Gerard & Doty (102) have obtained interesting results on oxygen metabolism during excitation, finding that nerves under the action of some drugs can conduct for long times without increase of oxygen consumption.

Initiation of the nerve impulse.—An important advance in the knowledge of the mechanisms of initiation of impulses was made when Hodgkin (124)

discovered that development of subthreshold activity underlies initiation of propagated impulses in nonmedullated nerves, a finding which Schaefer & Haass (199) later extended to the end plate. This subthreshold activity has the electrical sign of a localized depolarization, but it differs from a catelectrotonus in that it has a threshold and its intensity is not directly proportional to the stimulus. This phenomenon has been called local potential or local response. Its features and its significance are described and discussed most clearly by Hodgkin (126), Schaefer (198), Katz (141), and Blair (28). Its relevance to the process of excitation of medullated nerves is denied by Lorente de N6 (162) and by Tasaki & Takeuchi (216) but is maintained by Schmitt & Stewart (200).

The local response has been directly recorded in a single medullated fiber by Huxley & Stämpfli (136). The response appears only when the stimulus strength approaches 90 per cent of threshold. Reasons are given for considering it to be a biological response of nerve fibers and not an artifact due to surrounding connective tissue as suggested by Tasaki & Takeuchi (216). Del Castillo-Nicolau & Starke (64), recording from single fibers, found the same responses and clearly showed their relation to the spike. Their experiments, performed by stimulating and recording from a single node of Ranvier (the adjoining two nodes being anesthetized), show that excitation is easily evoked if the stimulating current is allowed to flow across a node, while no response is obtained if the stimulus is applied to an internode (65). Schoepfle & Erlanger (201), partially modifying previous statements (202), agree that a local response can be recorded from thin-stripped frog's nerves. In mammalian spinal roots, a cathodal local response can also be found, and this is compared to the potentials recorded by Hodgkin (124, 126) in axons of invertebrates [Rosenblueth & Luco (193)]. This response, however, relates to the propagated spike in a peculiar way inconsistent with the assumption that propagated excitation is initiated when the local response reaches a critical amplitude (126). A local response, developing in an exceedingly long time (hundreds of milliseconds) and comparable to the subthreshold activities demonstrated in nonmedullated nerves (125), has been recorded by Draper & Weidman (71) from spontaneously beating heart fibers and is supposed to be the mechanism underlying rhythmical activity of the heart. Emphasis of the importance of subthreshold activity in the initiation of impulses is also given by experiments showing that the repetitive excitation which originates in muscle spindles subjected to stretch is related to electrical signs of depolarization of the receptors [Katz (140, 142, 143)]. The height of the local response corresponds to the amount of applied tension and to the frequency of the repetitive discharge of impulses. Local anesthetics can abolish the impulses, leaving the local depolarization unchanged; crushing of the sensory nerve fiber between muscle and electrodes abolishes the slow wave. The shape of the spike recorded near the point of origin in the receptor may indicate that the sensory terminals are polarized more than the axons. When the tension is weak and afferent im-

pulses are generated irregularly and at low frequency, small decrementally propagated spikes ("abortive impulses") can be recorded in proximity to the terminals. These results directly confirm what Matthews had suggested on the basis of indirect evidence (173, 174).

The features of initiation of impulses in receptors have also been studied by a number of other authors, mostly with the use of techniques involving activation of and recording from single units and involving accurate control of all parameters of the sensory stimuli. Among such phenomena studied have been the responses of single stretch receptors during muscular contraction (131), the discharge of skin receptors and the influence of antidromic stimulation of the sensory nerve on their activity (114), the initiation of impulses in single Pacinian corpuscles (108, 109, 110, 203), the responses of the lateral line of fishes (206), discharges from the semicircular canals during angular acceleration or to sound and other stimuli evoking displacement of endolymph (103, 224 to 227) the responses of single retinal units responsible for the "on" and "off" effects (30, 69) and for the large unitary retinal discharges (195, 197), the activity of receptors in the frog's tongue (7), and activation of olfactory receptors mediating discrimination between different substances (1).

Important results have also been obtained with the use of artificial stimuli. Selective electrical stimulation of fibers of different type in stripped frog's nerves has shown that a significant relation exists between space constant of excitation [Rushton (196)] and conduction velocity (165). The stimulating ability of linearly increasing currents has been studied in single medullated fibers by Tasaki (212). Excitation has been shown to arise when the voltage reaches a certain liminal value, which is just slightly higher than rheobase, provided the gradient of the stimulating voltage exceeds a minimal slope (0.2 to 1.0 mv. per msec.). Latent periods of more than 50 msec. were observed in large motor nerve fibers of toads when the gradient was near liminal value. Studies of excitation induced by exponentially rising currents gave results consistent with these (214). The efficiency of square wave alternating currents of different frequencies for evoking nerve excitation was studied and discussed in relation to Nernst's theory of excitation (187) by Bruins, Duyff & Walter (49, 72). Tasaki & Sato (214) state that the results obtained with alternating current stimulation are not explained by the present theories of excitation, a modification of which is advanced. Technical problems related to electrical excitation of nerves with currents of different types were discussed by Hernando de Larramendi *et al.* (119).

The position of the stimulating cathode relative to a node of Ranvier has been shown to have great influence on the threshold of the response. Lussier & Rushton (166), studying the excitability of a single fiber without resorting to its isolation, have convincingly proved that the myelin sheath of the internodes is an almost perfect insulator [see also (65)]. Van Harreveld's observation of slow mobility of the potassium ion across the myelin sheath of nerve fibers is in agreement with these findings (228). Results

leading to the same type of conclusion have also been produced by Tasaki (213). By stimulating a single medullated fiber, immersed in Ringer, through a microelectrode, he found that the rheobase, as well as the threshold to brief (10 μ sec.) stimuli, depend upon the distance of the localized cathode from a node. The position of the stimulating electrode, besides determining threshold obtained, also strongly influences the time course of the local response brought about by subthreshold stimuli. A brief conditioning shock applied at a distance from the node produces there a change of excitability which follows a slow time course and attains maximum after considerable delay, but a shock applied directly at the node causes an excitatory process which grows and decays with a much faster time course. Since the myelin sheath can be expected to act as a leaky condenser (209), such delay and the slower time course can be ascribed to the time involved in charging the leaky myelin capacity. These results lead to the conclusion that the local excitatory state in the nerve fiber is nothing but the potential difference across the membrane of the nerve at the node of Ranvier. Further analysis and discussion of these findings which seem to be of great importance to the question of electrical excitation of nerves has also been produced, and more articles have been promised [Tasaki (210, 211)].

Axonal conduction.—The reviewers are not aware of any major changes in the concepts of axonal conduction. The theory that electrical current flow engendered by an impulse in one segment of the axon is sufficient stimulus to evoke activation of neighboring areas still rests on demonstrations offered by Hodgkin (123). It has also been confirmed that excitation does not propagate continuously along medullated nerves but jumps from one node to the next (86, 134, 135, 215, 229). An adequate review and discussion of this topic was given last year by Bullock (53). One of the favorite arguments opposed to the general validity of saltatory conduction has been based on the claim that medullated nerve fibers of the central nervous system do not contain nodes of Ranvier. Quotations 69 to 72 of Bullock's review (53) refer to recent evidence of the existence of nodes in the central nervous system. Huxley & Stämpfli (134) have now shown that nodes can be easily demonstrated histologically in the spinal cord of rabbits, and they maintain that none of the data on conduction velocity in different fibers and in various conditions contradict the saltatory theory.

Some results showing that electrical currents penetrate the fibers from Ranvier's nodes have already been quoted (65, 166, 213). Tasaki & Tasaki (217), confirming and extending previous findings by Tasaki & Takeuchi (216) and by Huxley & Stämpfli (134, 135), showed that the amplitude of the action potential recorded by means of a thin (5 μ) electrode from a single medullated fiber, depends upon the distance of the electrode from the node, and the observed data are in good quantitative agreement with theoretical expectation. This conclusion is contradicted by Laporte (150) on the basis of results obtained under the rather unfavorable experimental conditions of recording activity of a single fiber from a whole nerve trunk. The results

reported by Lussier & Rushton (166) show, however, that currents do enter and leave a nerve fiber exclusively at the nodes of Ranvier, even if the axons are not isolated.

Fry & Fry (97) have discussed the possibility that a mechanical disturbance, based on a piezoelectric or some such similar mechanism, may accompany electrical activity of nerve fibers and cause the known relations between fiber size and conduction velocity. An interesting approach to the problem of conduction of impulses has been made by Bullock & Turner (54) who found that conduction of impulses did not always occur according to expectation in single fibers of invertebrates. It was observed that on certain occasions conduction took place only in one direction or complete block of conduction occurred or the impulse was followed by after-discharge. Cases were also found in which the impulse died out in a certain region but was again generated at some distance as a consequence of the local activity present in and beyond the area of block. Repetitive stimulation is one of the experimental conditions leading to these conduction phenomena. Others are electrical polarization and drug actions. The degree of experimental abnormality was, however, moderate in most cases, and it was suggested that similar events may take place normally. Bullock & Turner point out that conduction in these conditions has clear analogies with synaptic transmission. Results on fatigue are also briefly reported (52). Magladery and others (167) have extensively studied conduction in the nerves of human beings.

The importance of the role played by acetylcholine in both conduction and transmission is again emphasized by Nachmansohn (182) on the basis of a wealth of experimental findings which have for the greater part already been mentioned and discussed (53). Granting that a radical revision of the old chemical hypothesis is necessary, his major argument in favor of the concept that acetylcholine metabolism is an indispensable factor in the generation and propagation of excitation is the finding that these cannot occur without cholinesterase. Since it is agreed that very little of the enzyme is sufficient for securing propagation of excitation, it would be interesting to determine whether the speed of hydrolysis of acetylcholine, which is still recognized to be necessary, can be attained when the enzyme concentration has reached the minimal values still permitting propagation.

TRANSMISSION AT THE SYNAPSE

There is a tendency to assume that the mechanism of transmission is the same at all synapses and, as a matter of fact, Feldberg (91) relies, in part, on this assumption in concluding that chemical mediation must operate in the central nervous system synapse. There are anatomical peculiarities of all the various synaptic situations, and the functional requirements of the systems are also somewhat different. It seems unsafe to assume, therefore, that there are not special peculiarities of each synapse or no special developments of certain of the common transmitting mechanisms characteristic of all synaptic situations.

New statements of the various theories of synaptic transmission have appeared through the year. Feldberg (91) has assembled evidence which he felt indicated there must be chemical mediation at the central synapse. Eccles (76) has dealt with the electrical theory of transmission in the monosynaptic pathway of the cord. Rosenblueth (191) has outlined his concept of both the electrical and chemical theory of transmission and, finding them not completely satisfactory, has formulated a new theory of transmission incorporating various features of electrical and chemical action. Lorente de Nó & Laporte have expressed the opinion that no theory thus far advanced has much to recommend it (164).

The reviewers do not agree with the concept that an electrical theory of transmission is completely untenable for all synapses. The elaborate concepts and evidence produced by Eccles (76) should not be lightly discarded. They do agree, however, that multiplicity of mechanisms are involved, that the electrical and chemical phenomena of transmission cannot be separated easily into primary and secondary phenomena, and that it is probably an incorrect approach to attempt to do so.

Artificial synapses.—Transmission across simple artificial junctions is discussed by Arvanitaki & Chalazonitis (12), and the possible analogies with phenomena of central transmission are analyzed. The main experimental result basic to this discussion is the finding [Arvanitaki (9)] that subliminal activity can take place in an area of a normal nonmedullated axon following arrival of an impulse at an adjacent point in another axon. If the "receiving" area is "activated" by chemical substances (e.g., 0.6 *M* sodium pyruvate), the arrival of the impulse of the adjacent axon can evoke generation of propagated, and eventually repetitive, excitation. The authors now give convincing evidence that normal somata have many properties in common with these activated nerve fibers, namely, high excitability to electrical stimuli and tendency to subthreshold oscillations of the membrane potential. In neurons, these oscillations can sometimes be autogenic, or they can be evoked by electrical stimulation or by chemical actions. In activated axons, the oscillations following stimulation can either be damped or have a tendency to build up gradually to supraliminal values, with the consequent possible result of delayed discharge. The effect of a stimulus on an oscillating axon can be shown to depend in part on its timing relative to the oscillating cycle. A multiformity of patterns of excitation can be brought about by rhythmical stimuli delivered to oscillating structures, the characteristics of excitation depending mainly on the relations between the frequencies of oscillation and stimulation. The variations of the pattern of excitation can still be increased in normal central transmission, because the effective stimulus applied to the postsynaptic elements will not always be a brief cathodal pulse. Due to the presence of after-potentials and to geometrical conditions, its shape will vary in different cases, and variations in the postsynaptic response will result.

These experimental conditions involve consideration of only electric

phenomena as possible excitatory agents responsible for transmission. Convincing arguments do support the assumption that such mechanisms are operating in normal central transmission. However, it should not be concluded from this that the mentioned agencies are the only possible excitatory factors in all physiological conditions. An example of a completely different mechanism underlying transmission of excitation, in a preparation which can be compared to an artificial junction, is offered by results of Habgood (114), who found that experimental antidromic excitation of a cutaneous nerve of frogs can evoke sensitization of neighboring skin receptors or excitation of nerve fibers adjacent to but not connected with the ones in which impulses were backfired. Accumulation of a chemical substance or of ions seems to be the most likely excitatory process in this case. How much this artificial situation can be compared to physiological phenomena of transmission cannot be stated. It seems, however, to suggest an interpretation of the dorsal root reflex (18, 19, 222, 223) with which both the experimental situation and the results have striking analogies.

Transmission at the neuromyal junction.—Although the mechanism of transmission at the nerve-muscle junction has not been agreed upon, some accord has been reached concerning certain aspects of the transmission phenomena. Several reviews of the situation have been published which outline the present state of our knowledge (83, 147, 192). First of all it can be said that the end plate has become in recent years more and more of a physiological entity with properties distinct from nerve and muscle, but at present it cannot be fully or accurately identified anatomically. Furthermore, the boundaries between the end plate and the muscle fiber are not defined physiologically; no effective membrane separates the two and potential changes spread freely in both directions (147). The validity of such a conclusion and of histological techniques and methods for studying synaptic structure has been discussed (29).

The specific end-plate properties have been summarized. It is well recognized that the end-plate region possesses special susceptibility to a variety of substances and environmental changes, particularly after denervation. Contradictory statements are found with respect to muscle sensitivity to the potassium ion, some saying that this ion acts equally at any place along a muscle fiber (147, 191), while others claim an end-plate sensitivity at least in certain species (50; 147, p. 599). Buchthal (50) has recently made a study of the action and interaction of various materials (acetylcholine, potassium, curare, magnesium, adenosinetriphosphate, etc.) on the end plate and muscle and has compared their action on the end plate with that of the nerve impulse. Additional investigations have been made of fibrillatory action in muscle, comparing the degree of this activity with changes in muscle excitability and the ability of the tissue to show the phenomenon of accommodation during the course of degeneration and regeneration following denervation (66, 67).

The main problem of neuromuscular transmission is no longer how the

muscle impulse is set up but how the end-plate potential (e.p.p.) is initiated by the nerve impulse (147). It is now pretty much agreed that in activation of a muscle by its nerve the membrane of the end-plate region becomes intensely depolarized, giving rise to the e.p.p., and by electrotonic spread the surrounding area becomes progressively involved until a critical stage and area of depolarization is established to initiate the propagated muscle impulse.

It is not adequate now to speak merely of depolarization of the end plate. According to Kuffler there is a cycle of changes at the end plate resembling the propagated disturbance itself (147). Rosenblueth (191) has described a variety of events which occur in sequence in association with activation of skeletal muscle by nerve stimulation. Other evidence may be interpreted to signify a complexity of events at the neuromyal junction (83, 148). There has been some consideration of the role of the potassium ion in transmission, but the exact role of this ion in neuromuscular transmission is not known (191).

It appears to be generally accepted that the depolarization of the end-plate region expressed by the e.p.p. is due to acetylcholine liberated from the motor nerve endings by the nerve impulse (83, 89, 147). The evidence advanced in support of this has been reviewed recently by Kuffler (147), and among the indicative findings the fact is mentioned that electrical stimulation of muscle fibers by means of microelectrodes has revealed no special sensitivity of the end-plate regions to this form of stimulation, as might be expected if the end plate were normally excited by the spike potential. Other evidence of this type has been presented by the above-mentioned and other authors in support of the idea that the nerve terminals release acetylcholine which acts upon the end plate of the muscle fiber.

There has been discussion of the mechanism of excitatory action of acetylcholine on the end plate (88). Evidence for the concept that acetylcholine works by rendering the membrane permeable to previously non-permeable ions, such as the sodium ion, and that the inward movement of this ion reduces the resting potential and creates the e.p.p. has been summarized and contrasted with that supporting the idea that acetylcholine itself, by moving inward across the membrane, depolarizes it (88). Sodium does potentiate the action of acetylcholine, possibly by entering the fiber as it becomes depolarized, and the mechanism of penetration is discussed. Although reduction of sodium in the solution surrounding the end plate does cause diminution of the e.p.p., it is thought to do so by changing the acetylcholine output from the endings, since the acetylcholine sensitivity of the end plate is unmodified. It is suggested that ACh^+ ions are released from nerve terminals, on activation, in exchange for Na^+ ions (89).

The function of the small medullated nerve fibers of mammalian ventral roots in muscle action has been discussed by Kuffler and others (130, 149). Small diameter fibers which conduct at 15 to 50 m. per sec. neither cause a detectable muscle contraction nor set up propagated impulses in ordinary

muscle fibers, but stimulation of these nerve fibers does set up contractile changes in the muscle spindles, which in turn influence the stretch receptor discharge. The effect of small-fiber excitation on this discharge depends largely upon the initial tension of the muscle spindle itself. Muscular contraction diminishes the effect of small fibers on the spindles due to the decrease in spindle tension following contraction. A single spindle receives innervation from several small fibers and a single small fiber innervates several spindles. Neuromuscular delay at the terminals of these small fibers is of the same order of magnitude as that of large nerve fiber junctional connections with extrafusal muscle. There is no information available concerning the role of the small-nerve system in reflex function, but the possibilities have been discussed, and this efferent system appears well-suited to act as a peripheral regulator of the proprioceptive reflex mechanism (130).

There have been other studies of neuromyal transmission and the function of the end plate. Spadolini (204) has suggested, on the basis of stimulation experiments, that the motor end plate presents a type of rhythmical activity. Nastuk (184) has recorded the e.p.p. of a single neuromuscular junction by use of microelectrodes inserted into single muscle fibers. It has been reported that *d*-tubocurarine in certain concentrations augments contractions of directly stimulated, acutely denervated muscle (20). After block of a phrenic-diaphragm preparation by physostigmine, tetraethylpyrophosphate, or di-isopropyl fluophosphate, it was shown that recovery of function preceded return of cholinesterase activity. The conclusion was that either cholinesterase is not involved in junctional transmission or such small amounts are required that they fall within limits of experimental error of assay methods (26). The action of prostigmine, acetylcholine, and carbon dioxide on the e.p.p. has again been studied (34). Buchthal & Engbaek (51) have examined the sensitivity of the neuromuscular junctions of man to intra-arterial injections of acetylcholine: 150 to 250 μ g. will produce a muscular twitch in normal man; 400 to 800 μ g. were required to affect myasthenic muscles, but following denervation the threshold is lowered. In a case of congenital muscular dystrophy the threshold gradually rose. Nastuk has applied acetylcholine to the region of the end plate for as long as 10 to 30 sec. In some cases intense depolarization (36 mv.) was maintained with an associated repetitive firing of impulses. Repolarization generally occurred some seconds after removal of acetylcholine, but occasionally it took place in the continued presence of the drug (185).

Decamethonium iodide produces a reversible block of neuromuscular transmission by causing a progressive depolarization of the end-plate region. Initially there is increased excitability and spontaneous activity of the muscle fiber. The depolarization can be removed and neuromuscular transmission restored, however, by application of anodal stimulation to the end-plate region. Application of a cathode deepens the block. Anodal currents also tend to reverse and cathodal currents to intensify the depolarizing effects of acetylcholine and tetanization of the end plate through the motor nerve

(55, 56). Neuromuscular transmission which has been blocked by deprivation of glucose can be restored by addition of glucose, hexose phosphate, lactic acid, or mannose, and it is concluded that there is an optimum glucose concentration for the synthesis of acetylcholine (179). Wiersma (231) has obtained evidence that in most decapod crustacean muscle nerves, single motor fibers possess two types of ending, a slow and a fast ending, which respond rather selectively to graded frequencies and durations of nerve impulse bombardment. Their functional significance is discussed. The electrical and mechanical events of neuromuscular transmission in the cockroach have been studied (190), and more work has been done upon the physiology of the electric organ (4, 5).

Ganglionic transmission.— This has been reexamined by Lorente de Nó & Laporte (151, 152, 153, 163, 164) in experiments performed on isolated sympathetic ganglia of turtles. Since only monosynaptic connections are present, none of the features of transmission found in these ganglia can be ascribed to internuncial activity. The authors confirm the claim (218) that in the turtle a synchronous presynaptic volley can evoke an early synchronous efferent volley, a late long-lasting discharge, or both. The minimal synaptic delays are of the order of 10 msec. and delays of more than 100 msec. have been observed. Clearly it follows from this that the delay of efferent reflex excitation is no measure of the number of synapses involved in the reflex path, a conclusion which seems worth emphasizing, since it is generally accepted that, in the spinal cord of mammals, discharges arising after delays of more than 1 msec. are necessarily due to excitation of polysynaptic paths. When curare is administered, the early synchronous response is abolished and the second one is more or less depressed. It then becomes evident that the late discharge arises from a slow potential [synaptic potential of sympathetic ganglia (81, 82)] revealing depolarization of the neurons. The latency of the synaptic potential is greater than that of the early discharge of untreated ganglia. From this and from study of the course of temporal facilitation, the authors conclude that curare acts mainly on the presynaptic terminals. When curarization is deepened a large positive wave appears following the synaptic potential. Very large doses of the drug evoke reduction in the size of the (negative) synaptic potential and an increase of the positive wave. According to the authors, this indicates that the positive phase is not an afterpotential arising as a reaction to the preceding depolarization, but it proves instead that it is possible for impinging impulses to, in certain conditions, result in increase in the membrane potential of the neurons. These results and conclusions are compared to the ones obtained by the Stockholm school on the spinal cord (21, 23, 24). It seems to the present reviewers that the relations between these two phenomena might instead be mainly formal. If it is true that the positive wave of the ganglion is not an aftereffect of excitation but is an expression of hyperpolarization directly induced by impinging impulses, it becomes important to determine how the conditions under which this happens relate to physiological conditions, since it would

be difficult to accept this suggested hyperpolarizing action of impulses in normal situations without very extensive justification.

The early discharge cannot be evoked by the local depolarization of the neurons because its latency is too short. It is supposed to be due to a brief excitatory action, which Lorente de Nó & Laporte identify with Eccles' "detonator action" (77). A later prolonged excitatory event is supposed to be responsible for evoking the synaptic potential, from which the late discharge originates. Thus, two different excitatory actions are accepted as present in monosynaptic transmission across a ganglion, and this conclusion is related to recent findings obtained in studies of the central nervous system.

Transmission at the central synapse.—The possibility that multiple mechanisms operate in physiological transmissions of the spinal cord has been considered in a number of recent papers. According to the reviewers, however, discussion of details of spinal actions should be preceded by clarification of some fundamental concepts which still are unsatisfactorily understood. Different results, leading to contrasting interpretations, have been obtained in studying the reflex activity of the spinal cord of mammals in old (17) and in recent researches. Furthermore, the results and interpretations reached through experimentation on amphibia are in agreement with the older, but hardly with later, series of findings on mammals. The main contradiction arises from the fact that the reflex discharge resulting from synchronous afferent excitation was originally observed by Barron & Matthews (17) to be of long duration and superimposed on signs of equally long-lasting local depolarization of the motoneurons, while it is now generally considered to have a duration of but a few (10 to 15) milliseconds. The presence of a local developing depolarization of the motoneurons is accepted by a few authors (78), but the excitatory process is supposed to have a negative phase of only a few milliseconds duration, followed by a long-lasting positivity. Barron & Matthews (17) considered the excitatory agent to be a long-lasting negative afterpotential of the terminals (dorsal root potential), but most authors believe the excitatory agent to be the incoming impulse itself and disregard the possible excitatory action of the slower wave. Independently of their possible participation in transmission, however, these slow dorsal root waves have been re-examined and analyzed in recent years, and one of the major conclusions of these studies is the statement that the primary origin of dorsal root potential is the post- and not the presynaptic element of the reflex arc (37, 84, 158). The evidence supporting this statement does not seem as yet to be crucial. In particular, since all the mentioned papers deal with the slow wave as recorded from a root adjacent to the root of entry of the impulses, it might be useful to point out that, though it is generally agreed that the propagation of the dorsal root potential involves activity of interneurons (73, 74), this does not necessarily rule out a presumed primary origin of dorsal root potential in presynaptic terminals of the segment of entry. Grundfest & Magnes (112) have now confirmed by means of excitability tests the reality of the small early waves which Lloyd &

McIntyre (158) had found to precede the negative deflection of the dorsal root potential recorded from a cut dorsal root. Their findings correlate very well with the known properties of the dorsal root potentials as described by Barron & Matthews, and much of their discussion is founded on an implied identification of these waves with Gasser's cord potentials [(101); see (37, fig. 10)].

Experiments planned to find the reasons for the mentioned contradictions in the results related to spinal reflex actions have led to the conclusion that positive afterpotentials of the motoneurons are present commonly only after barbiturate anesthesia. In decerebrated unanesthetized preparations the early local response is not followed by positivity, but by a further long-lasting wave of depolarization, identical to the one recorded in similar conditions by Barron & Matthews [Brooks & Fuortes (47)] which can be shown to be related to integrated reactions of the spinal cord (45). The dorsal root potential (as recorded from a cut root) is apparently not responsible for the earliest discharge, but is related to the long-lasting late wave as is the case in amphibia. No reason is found for supporting the view that only the discharge appearing after very short (1 msec.) central delay is of monosynaptic origin. Barron & Matthews' suggestion that all the comparatively early discharges are monosynaptic, while the late wave involves internuncial activity, is tentatively accepted (47). The results are considered to be in agreement with the view that more than one excitatory mechanism is operative in spinal transmission (48).

In frogs, an impressive amount of co-ordinated evidence has been collected by Bremer & Bonnet (37). These authors show in a convincing manner that the slow potentials which can be led off from ventral roots correspond to local responses of the neurons and are responsible for the generation of discharges of efferent impulses. The subthreshold local response presents all features attributable to Sherrington's central excitatory state, and it is justified to consider this local response to be the electrical correlate of this state. Also Bremer accepts the concept that two distinct processes underlie transmission at the level of the interneurons: a quick action, which is emphasized by the use of synchronous afferent volleys, and a longlasting process.

Other authors have used sensory stimulation for evoking reflex activity of the spinal cord of frogs. It has been shown in this way that proprioceptive reflexes are present in frogs and that proprioceptive inflow exerts facilitatory action on spinal reflexes (172), thus confirming prior findings by McIntyre (168). Muscular afferent excitation has been shown to give rise to a dorsal root potential resembling that following cutaneous excitation, while the ventral root potentials and the propagated discharges are different in the two cases. Selective electrical stimulation of nerve trunks yields similar results in frogs (99) as well as in mammals (47). This is an example of the fact that corresponding dorsal root potential and ventral root potential can be different under some conditions and suggests that they originate in different structures, a conclusion first emphasized by Bonnet & Bremer (31, 32) but

denied by these same authors recently (37). In the frog, however, no conclusion has been reached concerning the organization (mono- or plurisynaptic) of the reflex path subserving different peripheral sources, since the earliest observed discharges have delays of not less than 5 msec. (99). Further progress has been made in studies dealing with the early signs of reflex activity in anesthetized mammals. Brooks, Downman & Eccles (41, 42), analyzing the slow potentials rising in the motoneurons following ortho- or antidromic stimulation, find that the early negative phase is followed by a positivity which relates to hypoexcitability of the motoneurons. The size of this positive phase is correlated with the amount of activity preceding it in such a way as to justify the assumption that the positive wave is an afterpotential originating as a reaction to activity [see, however, Laporte & Lorente de N6 (152) for a different interpretation of positive deflections in ganglia]. Whatever the significance of these positive deflections in the spinal cord, they have thus far only been seen in barbiturized animals. It would be of great interest to clarify the mechanism of origin of this afterpositivity and its significance, especially in view of the fact that recent findings obtained by Eccles & Rall (85) on the effects of repetitive excitation probably relate to these afterpositivities. The authors have found that stimulation evoking propagated activity of only monosynaptic origin, in barbiturized animals, gives rise to summation of the local responses of the motoneurons and to facilitation of the propagated response only in the very early phases of stimulation. Within a fraction of a second the summated local response starts to decline and the efferent propagated discharges subside. A positive deflection follows the end of the stimulation. These findings lead to the conclusion that, in the monosynaptic arc, "spatial summation is much more important than temporal in generating the repetitive discharges that characterize natural movements." While this conclusion is in good agreement with other experimental results and with accepted theories, Eccles & Rall's other results and hypotheses present a difficulty of interpretation in view of the fact that sustained stretch of a muscle in (decerebrate or spinal) nonanesthetized animals results in a steadily maintained reflex contraction (154). Since stretch receptors supposedly (156, 157) activate monosynaptic paths only, this indicates that the conditions under which the reflex is not sustained are unphysiological.

According to the reviewers, the alterations in the properties of the activated central structures induced by the anesthetic are the most likely cause of the different results. A number of other findings are directly or indirectly in contrast with Eccles & Rall's conclusions and again suggest that the anesthetic is the cause of the failure to evoke sustained excitation. As mentioned above, positive afterpotentials, the concurrence of which would explain Eccles & Rall's results, are encountered only in barbiturized preparations, though they are not considered to arise only as a consequence of inter-nuncial block (47). Working without anesthesia, Hagbarth & Naess (115, 117) have found that the motoneurons of mammals can respond repetitively

to afferent muscular excitation, following frequencies up to 350 c.p.s., and emphasize the importance of anesthetics in determining the type of the spinal response. In frogs, repetitive muscular afferent excitation gives rise to sustained local response and repetitive discharges of the motoneurons (99, 172). Also in ganglia (where internuncial activity is out of question), long-lasting depolarization is evoked by repetitive presynaptic excitation (81, 152). It could still be maintained that unanesthetized animals present some type of "spontaneous" or induced internuncial activity and that this may evoke the conditions of facilitation of the motoneurons under which excitation can be sustained. If this is true, it follows that internuncial activity is essential for normal spinal actions and that only limited information concerning physiological mechanisms can be gained through experiments in which this activity is blocked.

Positive spinal potentials are again considered by Bernhard (22), who confirms and extends findings and interpretations previously reported by his school (21, 23, 24). In brief, the findings can be summarized by saying that stimulations evoking extension of a limb are followed by a positive deflection in a cut ventral root supplying the same limb, while a negative deflection is induced by stimulations evoking flexion. These opposite deflections can be evoked also by stimulations giving rise exclusively to subliminal excitation. How difficult it would be to interpret these findings in the light of the presently accepted knowledge is clearly emphasized by Bremer (35). It seems to the reviewers [contrary to recently advanced suggestions (176) and in agreement with unpublished observations by Matthews (175)] that these positive waves can be explained by operation of a mechanism completely different from the one underlying production of positive afterpotentials in structures under the influence of blocking drugs. If the assumption is accepted that, due to the steady inflow of impulses from receptors and centers, the spinal motoneurons are partially depolarized in normal conditions, it will also be acceptable that a decrease in the afferent inflow would result in decrease of depolarization, i.e., in a positive deflection. The only necessary postulation would then be that the stimulations which are followed by positivities evoke a temporary reduction of the impulses impinging on the motoneurons. One of the possible mechanisms is suggested and discussed by Barron & Matthews (17).

Problems related to drug actions on the spinal cord of mammals are dealt with by different authors. The actions of curare, strychnine, and barbiturates, administered singly or in combination, have been studied (25). In contrast with earlier findings (33), it is now extensively confirmed that strychnine enhances the so-called plurisynaptic burst more than the early synchronous reflex volley (46, 138, 183). Agreement also exists that barbiturates dramatically change the features of spinal reflex activity, but while some authors (78, 117) ascribe the effect of the drug mainly to blocking action on the interneurons, others (47) suggest that important additional actions contribute to the effects evoked by this substance.

INHIBITION

Until the mechanisms of integrative functions are better known, the term "inhibition" probably will be used in a vague sense to imply a blocking of activity in functional pathways regardless of the specific mechanism of this blockade (100, p. 185).

Thus, Martini *et al.* (113, 171) use "inhibition" to describe depression of cortical activity (preceded by spreading epileptiform excitement) resulting from stimulation of a "diencephalic inhibitory center." This phenomenon is obviously not identical with the inhibitory mechanism which blocks action in antagonistic muscle groups during reflex activity (75, 178). Poststimulation depression may be related to the spreading depression of Leão, which, however, may be an experimental artifact due to cooling, anoxia, or other abnormal conditions of the cortex (87). It may also be concerned in the suppressor reaction of Dusser de Barenne and McCulloch, many instances of which continue to be reported. Analysis of the mechanism (13, 169) of this depression has shown that the inhibition induced by stimulation of the brain-stem reticular formation does resemble in some respects, but not in all (reciprocal action), the well-studied inhibition involved in integrative activity of the spinal cord.

The theories of Eccles and of Gesell concerning the basic mechanisms of inhibition continue to dominate this field while the suggestions of Barron & Matthews seem to regain some favor. Gesell's concept that inhibition is due to the strategic position of certain nerve terminals on the soma, which permits their action to reverse a potential gradient of the cell and thus block its discharge, continues to attract some support (70, 104). Studies of the effects of direct current flow through the cord have led to the conclusion that the spinal motor neurons are directly excited or inhibited depending on the direction of the flow [(3); see (17)]. McCulloch, Lettvin, Pitts & Dell (178) have recently announced a new theory of inhibition which, though employing some of the basic principles incorporated in the concepts of Barron & Matthews (17) and Eccles (43, 75), visualizes a different anatomical peculiarity of the inhibitory pathway. Though it is stated that there are two ways of producing inhibition—"postsynaptic inhibition," which acts by increasing the threshold of the portion of the cell to be excited, and "presynaptic inhibition," which acts by decreasing or stopping the presynaptic volley that would otherwise excite the cell—only the mechanism of the latter type is described. Its essential difference from the Eccles' hypothesis is that inhibition is considered to be a phenomenon of the afferent or presynaptic terminals, and a block of fiber transmission is involved rather than a depression or stabilization of the soma membrane as in Eccles' theory. Here again, as in the theories of excitation and transmission, neurophysiologists are divided into two groups, one which believes that activity within afferent terminals is of primary importance to synaptic transmission, and another which believes that local excitatory and inhibitory processes accumulate on the soma of the motoneuron.

Eccles' hypotheses have again been expressed and brought up to date (75). He still believes that inhibition is due to an anelectrotonus created in the soma membrane by eddy currents arising from impulses or sinks blocked at a strategic distance from the motoneuron, but he states that his theories still contain defects, one of which is that it provides no satisfactory explanation of the intense and prolonged inhibition exerted by cutaneous afferents on extensor motoneurons. Although this theory visualizes inhibition as acting on the postsynaptic element, the impingement of the inhibitory anelectrotonus on the motoneuron is dependent upon a block in the afferent path (at a short-axoned interneuron) which prevents the impulse from reaching terminal knobs on the soma of the motoneuron.

Studies of inhibition of the monosynaptic reflex of the spinal cord are found to have application to other inhibitory phenomena. There is some evidence to confirm the concept of Brooks, Eccles & Malcolm (44) that inhibition acts on the soma but does not completely prevent the excitatory process from persisting or developing therein. Inhibition merely weakens or reduces temporarily its intensity to subthreshold levels. Dirken & Woldring (68) have stated that central vagus stimulation has a pure inhibitory effect upon the neurons of the inspiratory center but that this inhibitory action is exerted merely

by weakening the discharge of the neurons, which thereby keep some energy in store for the next discharge. A relatively high level of activity is retained in the cells so that but little additional energy is required for reaching the threshold.

The theories of central inhibition have also been considered in the light of results obtained on the ganglionic synapse. Eccles first suggested that there are preganglionic inhibitory fibers running to sympathetic ganglia (79), but he later abandoned this conclusion on the basis of other possible explanations of the phenomena observed (80). This concept of inhibition in sympathetic ganglia has been again announced by Lorente de N6 & Laporte (164). In an extensive experimental study and review of the work on ganglion transmission, they have stated certain conclusions concerning refractoriness and inhibition. These conclusions were based upon various types of evidence. First, by using preganglionic test shocks and preganglionic and postganglionic (antidromic) conditioning stimuli, it was found that recovery from antidromic conditioning was much faster. They felt that this difference could not be easily explained in terms of refractoriness but must be due to an inhibitory action of the preganglionic volley. Secondly, application of preganglionic test shocks at various intervals after preganglionic conditioning stimuli revealed no phase of facilitation but only a long-lasting depression during which more cells were blocked than had been fired by the conditioning stimulus. It was stated that since no facilitation preceded this depression, the positive afterpotentials of a local excitatory process (42) could not have been responsible. Thirdly, Lorente de N6 & Laporte showed that though the conditioning volley was followed by an afterpositivity, this response did not fully account for the reduction in size of the testing volley because the de-

gree of suppression did not parallel the time course of the afterpotential. In such cases, also, an inhibitory element was hypothesized. It was concluded by Lorente de N6 & Laporte that the inhibition was due to inhibitory endings but they state that "it has not been excluded that the *i* (inhibitory) action is referable to a reversal of the sign of the *s* (excitatory) action."

Lorente de N6 & Laporte (164) state that the inhibitory fibers establish an anelectrotonus in the motoneurons directly. They point out that since there are no short-axoned high-threshold neurons in the sympathetic ganglion the Eccles (43, 75) hypothesis cannot be used there and thus also should not be used to explain direct inhibition in the spinal cord.

Nevertheless, it seems acceptable to employ a hypothesis to explain how a preganglionic fiber can create the anelectrotonic effect, and the principle of block-at-a-distance is still a useful concept. The idea of a block at a branching of the preganglionic terminals (17, 178) combined with the Eccles idea of the anelectrotonus action on the motoneuron membrane would serve to produce the anelectrotonic inhibition required by Lorente de N6 & Laporte. These latter authors do state that though no doubt can exist that the "chemical" theory as originally elaborated cannot explain the facts of transmission, some modification might apply, and they point out that the inhibitory action of epinephrine (170) might be used in an explanation of inhibition in the ganglion. The general concept that inhibition can be best explained by a chemical mechanism is again advanced by Spadolini on the basis of experiments showing dual action of small doses of acetylcholine [(205; see also (180)).

Rosenblueth (191) states his opinion that all sympathetic preganglionic fibers to ganglia are excitatory but points out that Alvarez-Buylla (6) reported that the vagus contains fibers which on stimulation inhibit transmission in the superior cervical ganglion. The reviewers feel that the existence of inhibition in a sympathetic ganglion must be accepted if convincing evidence is obtained, but there is little to be accomplished by insisting that the mechanism of central inhibition must be identical to that which may operate in the superior cervical ganglion.

Other types of suppression and inhibiting blockade have been studied. The action of strychnine upon the phenomenon of intermittence of conduction in the dorsal columns of the spinal cord has been described (98). Changes in the excitability of spinal motoneurons following antidromic activation have been found to be associated with negative and positive afterpotentials. Though test antidromic impulses were blocked during the phase of afterpositivity, orthodromic test volleys showed little or no depression. An explanation of this phenomena was proposed (51).

One of the inhibitory phenomena which attracted most attention during the past year was that of autogenetic inhibition. This component of reflex self-regulation was studied particularly by Granit and his associates (105, 106, 107), Hagbarth & Naess (116), Brock, Eccles & Rall (39), and McCouch *et al.* (176, 177).

Brock, Eccles & Rall in their study of the action of afferent fibers in

muscle nerves have also stated their conclusions concerning the mechanism of the depressing and inhibitory actions of these nerve fibers. If a reflex discharge is evoked, the whole surface of the motoneuron passes through a prolonged (greater than 100 msec.) depressed phase associated with the positive afterpotential. Even if no reflex discharge occurs, a positive afterpotential of similar duration is still generated in the localized areas immediately under the activated synaptic knobs. There is a consequent depression of excitability, as determined by activation of these knobs, which is caused by the initial local excitation. This localized subsynaptic depression is not detectable by heterosynaptic testing as is the depression following reflex discharge. Refractoriness, the generalized depression following reflex discharge of a motoneuron and the localized depression following local activation of areas of membrane under synaptic knobs, is postexcitatory depression. True autogenetic inhibition is shown equally well heterosynaptically and homosynaptically and, when set up in a motor nucleus, is distributed to the motoneurons of all synergic muscles. Group I afferents of extensor muscles have no true autogenetic inhibitory action; there is a small inconstant inhibitory action of Group II afferents and a pronounced inhibitory action of Group III impulses, although the latter could not be demonstrated by homosynaptic testing.

A different approach was made by Granit *et al.* (105, 106, 107). They found that pure facilitation of the reflex contraction of a muscle (gastrocnemius) may be obtained by light stretch. Stronger stretch causes facilitation followed by inhibition, and the greater the tensile stress, the more effective the inhibition becomes. The afferent discharge evoked by contraction seems more prone to set up the late depression than the afferent discharge evoked by passive stretch. Granit suggests that the "silent period" of the knee jerk neurogram and the "lengthening reaction" are caused by autogenetic inhibition. These results have a parallel in the ones obtained by Hunt & Kuffler (131) with regard to the mechanism of activation and to the function of A and B receptors. Also, Granit's finding that inhibition can be obtained more readily when muscle contraction under stretch is evoked is consistent with the known and assumed properties of the receptors, since in these conditions B receptors are preferentially excited. On the other hand, his assumption that the silent period of tendon jerks is a consequence of autogenetic inhibition only seems to disregard the possible importance of the fact that A receptors are inactivated during such a period (62). The inhibition is not merely subnormality due to afterpotentials (41) because pure inhibition can be produced unpreceded by excitation or facilitation. McCouch *et al.* (175, 176) have produced evidence to support the generally held concept that these inhibitory impulses have their origin in the tendon spindles of Golgi. Granit (106) states that blockade of the monosynaptic reflex may be established by a combination of refractoriness, subnormality, and direct autogenetic inhibition, the latency of which is no greater than that of excitatory discharges. Granit offers no explanation of the mechanism of inhibi-

tion but states that it does act directly on the ventral horn cell causing a depressed state of excitability. His work, as well as that of Eccles and his associates, indicates that by techniques of selective stimulation the central consequences of autogenetic inhibition and postexcitation subnormality can be studied in isolation.

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THE SOMATIC FUNCTION OF THE CENTRAL NERVOUS SYSTEM

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Two events significant for neurologists occurred during the past academic year. The neurophysiologists presented to the December meeting of the Association for Research in Nervous and Mental Disease their recent contributions to the integration performed by the central nervous system. This new assessment of the function of that system was dedicated to Sir Charles Sherrington.

In June, the American Neurological Association presented a Symposium on the Brain and Mind. Although the relation of nervous tissue and mind is not a matter easily understood, some findings were reported which indicate the direction which may yield understanding. The cortex cerebri of man, for all its size, shows a greater structural uniformity and has fewer intercortical connections than does the cerebral cortex of other primates. The great mass or core of the brain stem, known collectively as the formatio reticularis, has begun to yield to the inquisition of modern electrical techniques an inkling of its function. Into this general region flow the activity of somesthetic and auditory impulses which are associated with "arousal to alertness or attention." The diffuse diencephalocortical projection system which affects the rhythmical electrical activity of the cerebral cortex may form, with descending systems which act upon the central reticular system of the brain stem, the neuronal network of activity which manifests attention and consciousness. Certainly, electrical stimulation of parts of the cerebral cortex which project into this system are followed by changes in the state of awareness. Following such stimulation of the anterior and rostrolateral surfaces of the frontal lobe, the conscious man may lose consciousness or be confused. Similar stimulation of the temporal lobe, when sensitized by eleptiform states, arouses specific auditory memories.

The latest presentation of the results of electrical stimulation of the cortex cerebri in conscious man beautifully fulfills the expressed purpose of the authors. Penfield & Rasmussen (1) have placed their findings on record for students of the nervous system to read, to compare, and to analyze. Their discussions are stimulating and their conclusions do not outstrip their data.

The neurologist will find Himwich's (2) *Brain Metabolism and Cerebral Disorders* understandable as well as readable. Complex enzymic actions are presented succinctly. The style is lucid, enlivened by original phraseology. To Himwich the brain is not a whole organ as is the liver; rather, its specialized parts are distinguished by a characteristic chemical activity.

Although the brain, like the heart, is considered by primitive peoples to

be essential for life, the Melanesians (3) recognized differences in its parts by their vulnerability to the warrior's club.

Several neurological papers are concerned with new contributions to old problems. The development of the weight of the brain of the guinea pig (4) does not follow that of the weight of the body as does the weight of its spinal cord. The results of a reinvestigation of transneuronal atrophy (5) substantiated the results of previous workers. Sensory nerve cells were present on the hypoglossal nerve in many mammals (6). An old experiment was rediscovered. Direct current polarization (7) between mouth and anus of the frog can selectively abolish or augment, depending upon direction of current flow, monosynaptic spinal reflexes. At last the first step toward the realization of the ultrasonic weapons of the comic strips has been taken. The frequency of 1 mc. of ultra sound paralyzed the hind legs of the frog (8).

Two groups of afferent fibers may serve the muscle fibers of a myotatic unit (9). The synergists of a given muscle are facilitated and its antagonists inhibited by monosynaptic action of its afferent fibers, the inhibition of the synergists and the facilitation of the antagonists by other afferent fibers which have a central latency of 0.5 to 0.6 msec. These afferents may be those which mediate the lengthening reaction and the associated action of antagonists.

The fasciculus solitarius of man (10) contains descending roots of n. VII, n. IX, and n. X, but not of n. V nor the ascending roots of C₁₋₃. The latter terminated in the medial part of the nucleus cuneatus and passed through the fasciculus solitarius to the commissural nucleus. No fibers from the roots of n. V were traced to the locus caeruleus or to the mesencephalic nucleus of n. V—a peculiar finding in the light of the results of comparable lesions to the cranial nerves of experimental animals.

The spinal cord.—Human paraplegics furnished the material from the majority of studies upon this part of the central nervous system. The studies of this region in animals have only the region itself in common.

The size of synaptic end bulbs upon three nuclei in the spinal cord were measured (11). The largest end bulbs were found on the cells of the chief sensory nucleus, i.e., upon the body of the smallest nerve cell of those studied. Bodian warned years ago that fixation in the mammals was so slow that all end bulbs were not preserved.

A re-examination of the constitution of the motor cell columns in the cat (12) has substantiated generally the conclusions of the older, classical work. The ventrolateral group in the lumbosacral cord supply the dorsal division of the ventral primary rami, the dorsolateral group, the ventral division. The reacting cells are quite standard when larger nerves are injured, but not when nerves to individual muscles are cut. Motor nerve fiber counts given by Sherrington's students are twice as large as the number of nerve cells reacting in the spinal cord after cutting the nerve to a given muscle.

No evidence of functional regeneration was observed after injury to the spinal cord of cats or of dogs (13), and yet some intrinsic spinal cord neurones traversed the lesion.

Three degrees of spasticity have been shown to result from ischemia of the spinal cord in laboratory carnivores (14). The most severe degeneration and one which was accompanied by pillar-like rigidity occurred in the intermediate horn and in the central areas of the ventral horn. The strong spastic state was associated with severe gliosis confined to the central region of the ventral horn, whereas the mild spastic state was associated with a mild gliosis in the comparable region. These results suggest that the inhibitors of the tonic state terminate in two definite regions of the spinal cord.

Growth in length and in area of cross section of the spinal cord of the macaque (15) seemed to be regulated in two ways: (a) as a proportion of the ultimate dimensions which are attained by the adult of this species, and (b) as a proportion of the dimensions of a total structure at a given time in development.

When properly facilitated, a ventral horn cell which can be activated by a monosynaptic shock without stretching a muscle, and one which can be caused to fire only by a stretch of the *M. gastrocnemius*, will fire a few milliseconds after an impulse is caused by stretch alone. Inhibition from autogenetic sources, when well developed, may stop discharge in either of these chosen neurones without regard for the refractory state (16).

The classical studies of Head and Riddoch have been beautifully elaborated by Kuhn's (17) physiological study of the function of the severed spinal cord in man. Although a progression of reflex activities developed which was comparable to those reported by Head and Riddoch, there were some individuals who never lost the reflexes of the perineum and genital area and others in whom the superficial reflexes reappeared within 24 hr. of the time the cord was severed.

The greatest difference lay in activity of the extensors of the trunk and legs. At six months after the injury, abrupt passive stretch of large muscle groups such as sudden extension of a flexed thigh was followed by contraction of the extensors. Pressure against the popliteal region of a relaxed lower leg was capable in the average patient of transforming the body musculature innervated by the severed cord into such a rigid framework that the patient could stand without support. Relaxation occurred in all of these muscles simultaneously. The patellar reflex was present and, in one-half of the patients, was vigorous. Even ankle jerks were obtained in 75 per cent of these men.

When the foot was put in "cold" water, these patients apparently without exception withdrew it by flexion of the lower extremity and yet when the skin of similarly injured patients was stimulated by cotton dipped in ether (18) almost one-half of them failed to respond.

The total areflexia and flaccid paralysis which once characterized this lesion was shown to be caused by interruption of blood supply or by a generalized degeneration of peripheral nerves.

Pain is sometimes a complaint of patients in whom the spinal cord has been completely severed. Such pain is poorly localized and described as burning, tingling, pins and needles, and stinging. Such individuals do not

undergo operations below the lesion without pain (19, 20). It is possible that afferents carrying pain impulses enter the spinal cord above the lesion. And as Foerster suggested, such afferents may travel in the sympathetic chain.

Generally, paraplegic patients have no particular pain problem. In some of them, the mean average threshold for perception of pain (21) was 230 ± 10 millical. per sec. per square cm. In three such patients with intractable root pain, which was relieved by lateral spinothalamic tractotomy, the thresholds for perception or for reaction to pain returned to normal range. Before the operation these thresholds were elevated! Even after prefrontal lobotomy, tests for cutaneous threshold for pain are more likely to be lowered than raised. In some cases (22) the test pain was thought to travel a route to higher centers, which the pathological pain did not take. It is this other route which constrains the neurologist to search further.

Recently, Sjöqvist (23) classified the tractotomies used for control of pathological pain. All sites of the spinothalamic tract have been severed. Such studies are instructive when results are given in detail (24). During one of these operations the central end of ventral roots were stimulated (25). Pain was evoked and referred to the appropriate segment at T₁₂, L₁, L₂, and L₃; but not at T₁₁, L₄, L₅, and S₁. Foerster reported finding pain afferents entering the spinal cord via the ventral roots.

There are individuals who complain not of pain, but the lack of it. Although the other moieties of general cutaneous sensibility are present (26), the tissues of the body are damaged without the usual warning. The skin contained the free endings assigned to pain.

Posture and progression.—In spite of the great work of Magnus and his collaborators, something remains to be learned. Stimulation of subcortical regions within many of the sites of large fiber bundles will stop walking in the unanaesthetized dog (27). Stimulation of the thalamic radiations or the region of the tractus rubrospinalis elicited movements of the extremities followed by characteristic changes of head and extremities (28) whereas the critical structures for the maintenance of body posture during progression were placed in the path of the brachium conjunctivum as it enters the thalamus (29). By changes in angle of the head of rabbits rotated on a turntable, one and the same motor response was thought to result from stimulation of different groups of receptors (30). Tonic neck reflexes, so long considered to be the response of stimulation of afferents within the muscles of the neck, were neatly demonstrated to arise in the afferents of the ligaments of the atlantoaxial and atlantooccipital joints. These reflexes were abolished by cutting the first three cervical roots at their exit from these ligaments or by bilateral circumcision of these ligaments in the presence of intact muscular and cutaneous nerves (31).

The cerebellum and its connections.—The spino-olivocerebellar pathway of cats terminates in the midline of the cerebellum between the fissura prima and the fissura secunda. The spino-olivary part is both crossed and uncrossed; its fibers ascend in the ventral funiculus. Neither the dorsal funiculus, nor

their nuclei in the medulla oblongata, contribute to this system (32). Also in the cat single fibers in the peripheral zone of the lateral funiculus yield electrical activity when the ipsilateral (not contralateral) muscles and tendons in the hind leg and tail are stretched. The border cells of Cooper and Sherrington which project to the brain stem and cerebellum (in the monkey) cannot be activated by nervous impulses arising in the periphery (33).

The regions in the cerebellum which receive connections from end organs serving tactile, auditory, and visual impulses are those which receive projections from tactile, auditory, and visual areas of the cerebral cortex and in turn project to them. To these the "motor" cortex adds its contribution. Indeed, every region which projects to the cerebellum receives something from it. Not only can localized movements be elicited by electrical stimulation of the cerebellar cortex, but also suppression or facilitation of cortically induced movements. In Snider's (34) words the cerebellar cortex is "a great modulator of neurological function." Time was required to displace the limit of its contribution to function, set by calling it "the head ganglion of the proprioceptive system."

The high spontaneous frequency of the intrinsic cerebellar cortex is never attained by spinal neurones or pyramidal units (35). Both waves and spikes originate from structures in the Purkinje cell, the granule cell layers of the cerebellar cortex, or both. Since the spike-forming mechanism is selectively susceptible to ischemia the waves must arise from a functionally different operating system (36).

The midbrain.—The midbrain contributes its own particular part to the reticular formation. Do the nerve cells in the oculomotor nucleus which were unaffected by the chromolytic reaction after division of the third nerve (37) contribute fibers to the fasciculus longitudinalis medialis or to some other part of the tegmental system? Into this general region three different hypothalamotegmental systems terminate. New connections, reported for the dorsal longitudinal fasciculus (38), substantiate Winkler's interpretation of it as the great visceral coordinating system of the brain stem. All of the important tegmental nuclei of the midbrain, the subthalamus, the centre median and the pons receive tectofugal systems (39). The vestibular nuclei contribute many fibers to the fasciculus longitudinalis medialis. When a semicircular canal was directly stimulated, the appropriate extraocular muscles were inhibited after that fasciculus was severed. On the other hand, after a transverse lesion at the level of the pons, the usual reciprocal inhibition of the antagonist was lost, and the correct contractile response persisted (40).

One of the by-products of Macht's (41) study of mesencephalic and bulbo-spinal cats was the finding that their thresholds of rejection of bitter, sour, and salty food were essentially similar to normal cats. Is rejection of unpleasant tastes a reflex, or is the midbrain capable of discrimination?

The basal ganglia.—The total volume of the basal ganglia increases as the primate scale is ascended (42). On the other hand, the relatively large

caudate nucleus of prosimians decreases and the putamen increases as the primate scale is mounted.

Recent studies of the fiber connections of these great nuclear masses (43) have not revealed any new and startling relationship. Only large lesions of the nucleus caudatus produce severe loss of coordination of progression (44).

In a bilateral symmetrical necrosis of nerve cells in the putamen and nucleus caudatus, painful stimuli may arouse the patient (45). Tone alternated from greater to less than normal. Although involuntary movements occurred occasionally, voluntary movements of trunk, extremities, and of those of speech were absent. Tremor was not mentioned.

Upon the theory that inhibition from area 4s is carried to lower centers via area 6, surgical intervention in severe cases of paralysis agitans attempted to cut the U fibers between these cortical areas. In only one patient was 4s located and stimulated with the gratifying result of reduction in rigidity and in movements. In this individual there was improvement, but in the remaining eight, no clear cut reductions in symptoms were discovered (46).

Two other types of surgical intervention for the rigidity and tremor of this disease were used this year. The rationale of each was good. In a case of bilateral Parkinsonianism, characterized by rigidity and negligible tremor, a cut was made in the region of the ansa lenticularis on the right. The rigidity of the left extremities was not diminished, that of the right was. The patient became able to use the right extremities in ways which were impossible before the operation (47). Using Walker's operation, the corticospinal system was interrupted in the basis pedunculi with the result that the tremor decreased and, in spite of the hemiplegia, the patient was able to walk and to use his hand in a satisfactory manner (48).

The most astonishing and stimulating attempt to control the tremor and rigidity of Wilson's disease occurred this year. Ever since Wilson's description of hepatolenticular degeneration, the simultaneous injury to liver tissue and to that of the basal ganglia, especially the putamen, has puzzled neurologists. Several years ago copper was found in the liver and the brain of patients dying of this disease. Two years ago Cumings suggested that BAL (2,3-dimercaptopropanol) might increase the excretion of copper in the urine. Cumings (49) reported in the March issue of *Brain*, and Denny-Brown (50) before the June meeting of the American Neurological Association, that excretion of copper was followed in some patients by such a marked decrease in the tremor that even the bedridden could walk. This miracle may be short-lived as Cumings reported. Nonetheless, it is the first hope offered those suffering from an increasingly debilitating disease.

The diencephalon.—The nature of adaptation reported for laboratory animals without a neocortex might not be what it is, were such a preparation made. So far, all such animals have also lost part of the basal ganglia, the thalamus, and the old cortex (51).

In the opossum electrical afterdischarge can be prevented from spreading from one stimulated hemisphere to the other by sectioning both the anterior

commissure and the diencephalon, not, however, by cutting either one alone. When both are severed, a minor augmentation of the activity of the non-stimulated cortex occurred (52), perhaps via the few neopallial fibers which in some marsupials lie dorsal to the psalterium.

Search continues for fiber relationship and function of the region of the subthalamus and of the hypothalamus. Tremor at rest was produced by electrolytic lesions in Forel's field H. This tremor disappeared in one animal after removal of the contralateral rostral half of area 6 and the dorsal half of area 8 (53). Stimulation of the lateral part of the posterior hypothalamus (54) facilitates vasomotor and respiratory reflexes. These reflexes can be inhibited by stimulation of the medially lying reticular system. In other words, the medial formatio reticularis inhibits visceral as well as somatic activity.

Neither the subthalamic nucleus nor the substantia nigra contained chromatolytic cells after removal of the diencephalon (55). The hypothalamus of the guinea pig receives direct fibers from the optic nerve (56).

The corticothalamic connections in the brain of the cat are reciprocal (57). Each cortical area which has a principal projection to a thalamic nucleus, or nuclear group, receives fibers from that nucleus. Besides these loop circuits, each of these cortical areas is also the origin of a diffuse projection to nuclei which do not return fibers to it and therefore do not form loop circuits.

The hypothalamus received corticofugal fibers from the frontal and limbic lobes, from the orbital, sensorimotor, and auditory cortices. Extrapyramidal fibers stem from all cortical areas, except the basal orbital region, and share as terminals one or more of the motor nuclei of the thalamic or midbrain tegmentum. The corticotectal fibers arise from the visual area, parietal association cortex, and the auditory cortex.

The diffuse thalamic projection system stems from five nuclear groups, the centre median, the intralaminar nuclei, the anterior nuclei, the nucleus ventralis anterior, and the anterior pole of the reticular nucleus (58). Excitation of any one of these nuclei of diffuse projection evoked a sweep of recruiting waves in all of the other nuclei, of which the nucleus ventralis anterior is the single most intense receiving focus. Excitation of the reticular nucleus produced responses in the lateral part of the central nucleus, the nucleus lateralis posterior, and the pulvinar. This group of thalamic nuclei constitutes a neural unit which, oriented caudorostrally, discharges as a mass.

The cortical receiving areas for this thalamic projection system are well localized and separated completely from the somatic, auditory, and visual receiving areas. They are, in part, the association areas separating these cortices. They also overlap the "motor" cortex, sweeping, laterally, along the ventral and anterior margin of the cortical surface and, medially, from the cruciate sulcus caudalward into the cingulate gyrus. Certainly, this system is structurally fitted to exert a direct mass influence on the areas which receive it.

In man, two of the thalamic nuclei, which in the cat contribute to the

diffuse thalamic system, the nucleus ventralis anterior and the reticular nucleus, contain the cells of origin for a thalamic projection to area 6 (59).

The telencephalon.—Neither the pallium nor the telencephalic vesicle of tailed amphibians (60) grows normally when its relation to the brain stem is interrupted. Neglecting the great fissures of the cortex cerebri (and consequently a great deal of it), the area of the outer surface of the cerebral cortex in man increases about 100 per cent between birth and the sixth year of life (61).

For several years Flexner (62) and his collaborators have studied the biochemical and physiological morphogenesis of the cerebral cortex in the fetal guinea pig. Not until the forty-sixth to the forty-ninth day does the fetal cortex manifest spontaneous electrical activity. Also, at this time, five days after neuroblasts have differentiated into neurones and after an abrupt rise in activity of the enzyme, apyrase, permeability of these neurones to sodium ions increases. Between these two dates (63) contraction of skeletal muscles may be elicited by electrical stimulation of the fetal cortical surface. This critical period occurs after two-thirds of the gestation span is past. In the macaque, however, Hines and Boynton elicited contraction of skeletal muscle from the cortical surface on the sixty-sixth day of a 165-day gestation period.

Characteristics of the cerebral cortex.—Fashion frequently characterizes analysis of groups of phenomena. Some fashions constrain their agents to destroy the old before the new is created. It is popular to criticize, without appreciation, the colossal task performed by the older students of the cyto-architecture of the cerebral cortex. The new cortical map finds the maxima of structural alteration gradients exactly where every first-year medical student can see them, even in Nissl preparations. And the more observant of such students are able to find some of the regions designated as areas of minimal change (64).

Isolated cortex of the cat is electrically inactive (65). An electric stimulus evokes a surface negative response which spreads in all directions in a radius of less than 1 cm. at a velocity of 2 m. per sec. A surface positive response followed the negative wave when the stimulus was 30 per cent above the maximum and travelled at a velocity of 10 to 20 cm. per sec. These findings resemble those of Chang (66). The surface negative deflections cannot be boosted by supraliminal stimuli. Rather, as the intensity increased, the density gradient enlarged. Pushing the electrodes into the cortex about 1 mm. caused the first component to become surface positive; the second remained unchanged. These potential changes were local, traveling not more than 5 mm. at a velocity of 1 m. per sec. in the cat and 0.6 to 0.7 m. per sec. in the monkey. Besides these two potentials, the repetitive discharges of the cortico-thalamic circuit can be elicited by direct stimulation of a sensory cortex (67).

A word of caution concerning interpretation of results of strychninization of the cortical surface appeared in two papers. Although the majority of neurones "fire" for strychnine, not all do (68), so that negative findings do

not exclude direct neuronal connections. Strychine (69) seems to have little effect upon the dendritic potential of cortical neurones. Rather, strychnine seems to synchronize the discharge of cortical neurones.

Using the method of strychninization intracortical relations of the cortex buried within the intraparietal and principal sulci of the monkey's brain were mapped (70). The unusual findings were of reciprocal frontal and parietal connections.

Caution should be exercised in the interpretation of suppressor areas under experimental conditions which facilitate the spreading depression of Leão. For that depression can be reliably demonstrated (71) by long exposure of the cortical surface to the air, by radical dehydration, and by cooling of the region in cat and monkey.

The rhinencephalon.—In spite of a maldeveloped rhinencephalon revealed at death, the individual in life was sharp, intelligent, and lazy. He was easy-going, never lost his temper, and withal had a normal sense of smell. The stria terminalis was normal; the fimbria and fornix, absent (72). The hippocampus has lost its ancient assignment. Were men like Bard and Mountcastle's cats, the friends of that individual could well be glad that it was not the stria terminalis which was missing.

Search for an anatomical difference in the brains of whites and Negroes (73) revealed none in the secondary olfactory areas.

If the hippocampus is not the small brain, what is it? The evoked potential technique answered (74) that in the cat it received auditory, optic, and somesthetic impulses and that the cingulate gyrus received both optic and auditory stimuli.

The anterior cingulate gyrus has been re-explored, with results which are similar to those reported previously (75). Intercortical afferents from areas 4, 6, 8, 9, and 10 enter this region but none leave it for subcortical reticular centers. How does the inhibitory action, observed to follow its stimulation, reach the reticular formation of the brain stem? Vascular and respiratory responses similar to those elicited from the anterior cingulate gyrus were produced by electrical stimulation of such varied regions as the tip of the temporal pole, the posterior orbital surface, the anterior insula, the anterior perforated space, and the subcallosal and precallosal gyri (76).

The "motor" cortex.—The contribution of the several parts of the frontal agranular cortex has been reassessed in trained monkeys (77). Return of function to the affected extremity was the focus of study. The "paralyzed" side may also set its pace. In synchronization of bilateral spontaneous movements made by a patient with hemiparesis (78), the intact limb loses its previous rhythm. When, however the affected side is activated alone, a strong synkinetic fixation occurs in the other extremity. If called upon to perform rapid alternating supination-pronation of both forearms, the facility of the normal side is greatly decreased. The normal extremity is not unequivocally normal. The early studies of the results of such cortical loss by the French clinical neurologists (Dejerine and others) found some evidence

of spasticity on the normal side. The physical therapist (79) evokes mass movements to help a patient use a paralyzed muscle; for muscles, which cannot be used in discrete movements, can be used in mass movements. Or again, maximal stimulation of mass movement patterns results in marked and prolonged relaxation of spasticity, muscle spasm, or even the rigidity of Parkinsonianism. These findings should be elucidated.

The removal of one hemisphere in adult man was followed during the brief span of survival by paralyzed extremities (contralateral) by hypoactive deep reflexes and in one of four patients by spasticity (80). A similar operation with the addition of the putamen was used (81) in children born with unilateral spastic hemiplegia (plus in some cases, choreoathetoid movements) with surprising results. After operation these children learned more easily, even in the motor sphere. Not only was their behavior improved, but there was also a profound betterment in mentality. Without as radical a treatment, improvement in the hemiplegia of three individuals, born with abnormal motor cortices, followed ablation, not only of all the abnormal sensorimotor cortex, but also of all motor cortex above the fissure of Sylvius. Such patients began to use their hands and could feed themselves (82). These findings must not be forgotten when the function of the precentral gyrus is considered.

In an analysis of loss of motor function resulting from cerebral lesions (83), topographical representation of muscular paralysis was considered relative and paralysis of single muscles (which Foerster reported) was denied. The respective lesions may not have been similar: for it is difficult to believe that Foerster did not see what he described.

Not only does proprioceptive activity modify the results of electrical stimulation of the motor cortex (84), but also that of the vestibular nerve (85). Section of this nerve abolishes or diminishes the elicitation of muscular contraction by threshold stimulation of that cortical surface. When separated from such afferent modulation by decerebration, the threshold for activation of a particular muscle, within a particular animal is constant, when the pyramids at the level of the medulla oblongata are stimulated under controlled experimental conditions (86).

Stimulation (by implanted electrodes) of the motor cortex which lies within the sulci elicited responses which summated with spontaneous movements, resulting in dysmetria (87). Prolonged and repeated excitation of a single point may be followed by periodic recurrence of a response, for several hours after cessation of stimulation.

The recent reports of the results of electrical stimulation of the motor cortex (88, 89, 90) appear to be directed toward obtaining evidence which can be used to prove the mosaic hypothesis untenable, rather than toward analyzing the function of this cortical apace. (The literature cited is peculiarly selective.) The motor cortex is versatile. Its neurones will transmit many types and parameters of the electric current. Those used here, even at threshold, seem incapable of eliciting contraction of single muscles. Indeed, using one of them (88) "no evidence of a fundamental difference in

behavior of areas 6 and 4 and also that part of the postcentral gyrus adjacent to 4" was discovered. The Cambridge inductorium did better than that. With a square wave stimulator the region from which "a flick of the opposite thumb" was produced could, by varying the parameter of stimulation, be enlarged to cover large areas of the arm and leg area. Would this current applied to the leg area, after removal of all of the arm area, produce contraction of muscles of the thumb? It is possible that such a result might occur, because stimulation of this region, after cutting the pyramids, elicits contractions of muscles of trunk and extremities, including at times those of the digits.

The conclusion reached by these workers is that the mosaic hypothesis is not rigid and absolute. Those who found the mosaic considered it the result of observations, rather than a basis for an hypothesis. The sine wave current, the frequency and the intensity of which can be controlled, is able to elicit contraction of single muscles and parts of muscles. When the whole region was so stimulated, a pattern of parts of somatic musculature of the macaque was topically arranged upon it. The fact that removal of small areas is not followed by permanent loss of use of the part so represented does not mean (a) that the mosaic was not obtained, nor (b) that discrete fibers do not terminate in the vicinity of a particular ventral horn nucleus. Nor can the quoted finding that Marchi degeneration following ablation of parts of the arm area (in the monkey) was found in the lumbar cord be used against the existence of a topical localization within the precentral gyrus. Discrete use of somatic musculature depends upon fixation of muscles of the girdles, as well as those which in their fixation free other muscles for isometric contraction. Muscles, which in the adult monkey fix a part, actively contract in the infant when the distal muscles of the extremity are voluntarily used. Stimulation of a cortical point, so located that in the adult it yields contraction of distal musculature only, cause, in the infant, contraction of proximal musculature as well.

Further, the finding of a supplementary motor area complete for extremities, trunk musculature, and face, upon the medial surface of the frontal lobe in both man and monkey (91) vitiates conclusions drawn from small lesions of the precentral gyrus.

The prefrontal areas.—The understanding of the function of prefrontal areas in man has been aided by the results of prefrontal lobotomy (92). In Freeman's report (93) no one of his patients has done anything creative since lobotomy. Incisions made far anterior interfere with fantasies and creative skills; those far posterior are fatal, because of visceral and trophic disturbances (94); whereas, between, the deficits in personality range from "barely perceptible to barely tolerable."

Brickner's (95) patient A has come to necropsy. No dense adhesions were found between the frontal lobe stump and the dura. No areas of softening of the remaining tissue and no evidence of impairment of the residual blood supply was discovered. For 17 years following the bilateral frontal lobectomy,

the picture of inability to grow and mature in his social environment remained.

Bilateral lesions made in the anterior thalamic nuclei in psychotic patients diminished their state of excitement (96). This nucleus, however, is not involved in the retrograde degeneration which follows prefrontal lobotomy, unless the knife severs fibers from the gyrus cinguli. It is the medial nucleus which projects to those areas, especially Brodmann's 8, 9, 10, 11, 45, 46, and 47 (97).

The frontopontine tract was followed in five human brains, whose owners suffered prefrontal lobotomies (98). This system lies dorsally in the rostral part of the internal capsule and medially in the pes pedunculi and terminates about the medial cells of the pons.

The posterior orbital surface of the monkey's brain (99) sends corticifugal fibers into the nucleus caudatus and into the paraventricular and ventromedial nuclei of the hypothalamus. The former acts upon respiration; the latter, upon arterial pressure.

Cortical sensory areas delimited by evoked potentials.—With this method of exploration vestibular impulses have yielded a cortical locus in the cat (100). This locus is similar to the polysensory area into which auditory, proprioceptive, tactile, and vestibular impulses project (101). Auditory areas I and II have been extended to include two regions upon the posterior ectosylvian gyrus (102). Somatic interaction seems to take place in Somatic I and II at cortical and subcortical levels (103). Visual areas I and II in the rabbit present a binocular coverage without a superposition of corresponding cortical areas (104).

Two types of response are recorded from the cat's visual cortex when the optic nerve is stimulated (105). But in higher mammals, especially in those which seem to recognize color, a triple conducting system of large, medium, and small thalamocortical fibers is present. The small cells described years ago by Henschen in the lateral geniculate body of some monkeys and assigned by him to color vision might be the origin of one of these systems.

The response evoked on the postcentral gyrus of man is a simple diphasic potential change of 20 to 35 msec. duration (106). The positive deflection has ranged from 50 to 150 mv. When the peripheral area of skin activating a cortical point is compared with the area to which the patient refers following cortical stimulation of that point, there is satisfactory correspondence. Such is the advantage of studying man.

The optic system in man.—It is unusual to discover degeneration in peripheral neurones following a cortical lesion. Three and one-half years after a bilateral injury of the occipital lobe, which spared the macula, the first indication of optic atrophy was observed. This atrophy of the optic disc followed the brain loss as interpreted from the residual visual fields plotted four months after injury (107). In perimetrically blind fields (108) man, like Klüver's monkeys, can perceive a luminous object in complete darkness. Form was not perceived. Movement was appreciated in the frontoparallel

plance, not in the parasagittal. Subjectively these abilities are of little value; for without form, all objects remain indefinite and meaningless.

The higher cortical functions.—The deficits in retention of learned discrimination were studied after lesions of the prefrontal and posterior "associative areas" in the macaque (109) and of the latter alone, of the temporal, and of the parietal lobes (110). It is a pity that the lesions were not more discrete.

The recognition, interpretation, and localization of multiple cutaneous stimuli are, indeed, a learned process. Before the sixth year of age children recognize only the more proximal of two separate single cutaneous stimuli. Proximal dominance persisting past the sixth year is presumptive evidence of mental retardation (111). This phenomenon is also found in adults with lesions of the parietal lobe. Since the more rostral of the two stimuli extinguishes the more caudal, Cohn (112) has sought and found no satisfactory explanation for this rostral dominance. In the first place, patients with lesions in the cortex cerebri find it difficult to pay attention to more than one event at a time. The stimulus which dominates is the one which travels the shorter distance and should, therefore, arrive before the more caudal stimulus does and thus claim the limited interest of the patient.

The displacement in localization of two sensory stimuli seemed to follow a definite order (113). One stimulus was reported immediately and correctly, the other denied or vague. In patients with severe mental symptoms, but no sensory defects, stimuli on hand and face were displaced to face, to thigh (hand resting on it), and into space. In patients (a) with unilateral sensory disturbances, the displacement occurred on the affected side; and (b) with bilateral sensory disturbances, the predictable direction was determined by the side of affected sensation. Pinprick plus a tactile or a vibratory stimulus was not recognized.

After removal of the right postcentral gyrus for pain in a phantom limb (114) proprioceptive moieties of sensation were lost in the stump of the left arm or in that of the left leg. Those of general cutaneous sensibilities remained. But when two cutaneous stimuli given simultaneously on symmetrical parts of the left arm and of the right arm or on homologous areas of the left leg and of the right leg, only the stimulus on the right arm or right leg (i.e., the normal limb) was recognized.

When single cutaneous stimuli were given the left upper extremity affected by a diffuse disease of the brain, the patient located these stimuli upon the homologous region of the right upper extremity (115). Although the patient knew when an object was placed in his left hand, he could not name or describe it and looked for it in his right hand. He not only ignored the environment on his left, but he was unable to show the left thumb. He said he had two thumbs; he could demonstrate the presence of only one, the right.

The neglect of the left side of the body may include neglect of the left half of space. In spite of normal sensibility on the left, when tested simul-

taneously with finger movements, a left hemianopsia was present (116). Sounds were located on the right. Of two bilateral simultaneous stimuli, nothing was felt on the left. There was, however, some loss of position sense in the left fingers and asternognosis on the left.

The extinction of general cutaneous sensibility is not necessarily restricted to the left; but reports of neglect of one-half of space or of knowledge of the body scheme suggests definite laterality. The laterality is frequently explained by the fact that when the lesion is on the left aphasia blots out communication necessary for examination. And yet why is there no report of such a patient choosing the left of two doors? It is significant to learn that right-handed patients (117) with aphasia were able to imitate the movement of the examiner with the left, not the right side; and those with hemiplegia and aphasia can point with the right hand to the left side of the body, but not with the left to the right. Paralysis was not, therefore, a limiting factor.

The localization of stimuli upon the surface of the body demands knowledge of its separate parts and is not entirely a function of a single peripheral afferent system. In some of these studies proprioceptive sensibility was cited as impaired and general cutaneous sensibility as almost normal. The exact contribution of these facets of somesthetic sensibility to the development of the body image is not entirely clear. Head made a neat distinction in a patient in whom a cord lesion had destroyed proprioceptive sensibility. He was unable to localize on his body, by pointing, the site of the tactile stimulus given; but, he could describe rather accurately, where it was. The patient had lost knowledge of position in space of his extremities; he had retained his body image.

The phantom limbs may be the result of retained body images. Phantom limbs may follow amputations of extremities in children of six or seven years, not before that age (118). In 2 of the 24 studied, a phantom appeared about two years after removal of an extremity. It is peculiar that the development of the body image included a part which was not present.

Three reports of unusual discrete losses, worthy of detailed study, have been published—an auditory agnosia (119), an agraphia, without aphasia (120), and in a deaf mute, an aphasia, which was confined to finger spelling (121).

The orientation of the body self within extrapersonal space is frequently lost after injury to the right occipitoparietal region (122). The losses of orientation include the ability to dress oneself, to find the way home by taking correct turns, even if they are left, and to diagram (not to describe verbally) relationships of objects in space. The failure is not one of recognition and naming of parts; it is, rather, one in the creative sphere. In the creative sphere a part is recognized as itself and also as having a place in a whole, which is an idea.

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VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM¹

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CEREBRAL CORTEX

New data relative to the influence on visceral functions of impulses emanating from the cerebral cortex have been reported by various investigators. In dogs under chloralose-urethane anesthesia, as observed by Babkin & Kite (1, 2, 3), stimulation of the anterior portion of the cingulate gyrus resulted in inhibition of the rhythmic movements of the pyloric antrum. Stimulation of the orbital surface of the frontal lobe usually resulted in inhibition, but sometimes in acceleration, of these movements. The vagus center appeared to be depressed by the inhibitory cortical impulses. The vagus impulses to the pyloric antrum and the pylorus, consequently, were weakened. Ablation of the cingulate gyrus bilaterally resulted in a moderate increase in the rate of contraction of the pyloric antrum. Antral motility was further increased following transection of the brain stem at the intercolliculomesencephalic level. The increase in the antral motility caused by ablation of the hypothalamus was not altered by transection of the brain stem. In experiments reported by Babkin & Speakman (4), stimulation of the insular-orbital region and the subgenual portion of the cingulate gyrus resulted in inhibition of motility in the pyloric antrum. Motor responses in the gastrointestinal tract of the cat elicited by stimulation of the anterior sigmoid gyrus and the anterior olfactory lobe have been reported by Ström & Uvnäs (5). Data reported by Clark & Meyer (6) indicate clearly that the conduction pathways between the cerebral cortex and the hypothalamus are more abundant than has been assumed on the basis of earlier studies. Some of the cortical areas concerned are more abundantly connected with autonomic effector mechanisms than others.

Marked alterations in visceral functions following leucotomy have been reported by Pötlz (7) and by Frowein & Klar (8). The immediate effects of such an operation include increased peripheral blood flow, abolition of the hypothalamichypophyseal reactions, incontinence of the rectum and the urinary bladder, and alterations in the number of white blood cells. These functional disturbances continue beyond the immediate postoperative period. On the basis of changes in body temperature in schizophrenic patients following prefrontal lobotomy, Buck *et al.* (9) concluded that the preoperative abnormalities in these patients represented the results of disturbing influences of the prefrontal cortex on lower autonomic centers.

On the basis of an extensive study of the effects of direct cortical stimulation in man, Penfield & Rasmussen (10) advanced the conclusion that the

¹ The survey of the literature pertaining to this review was concluded in June, 1951.

digestive functions, including salivation, swallowing and gastrointestinal motility, taste, and gastrointestinal sensitivity, are extensively represented in the cortex on the convex surfaces of the cerebral hemispheres and the insula. The cardiovascular, the sudomotor, and the pilomotor systems do not appear to be strongly influenced by impulses emanating from these cortical areas.

Bilateral stimulation of the rostral portion of the cingulate gyrus in man, as reported by Pool & Ransohoff (11), resulted in alterations in arterial pressure, pulse rate, and respiration. Data reported by Smith (12) support the assumption that the cingulate gyrus plays a more important role in the regulation of visceral functions than had been formerly suspected. The responses elicited by its electrical excitation extend beyond the realm of olfactory function. The cingulate and the pyriform cortical areas probably form an important part of the neural substratum of emotional expression and behavior involving both visceral and somatic reactions. Both these areas are intimately related to the hippocampus through abundant fiber connections. These fiber connections provide an anatomic basis for the assumption that the hippocampus and the fornix form part of a circuit through which a functional cycle is maintained between the hypothalamus and the neocortex. This circuit, as outlined by Clark & Meyer (6), appears to be made up of the hippocampus, the fornix, the mammillary body, the anterior thalamic nuclei, the cingulate gyrus, and the cingulum. It probably constitutes an important part of the mechanism of emotional integration. Intimate interrelationships of the rostral portion of the cingulate gyrus and the orbital gyrus, and the insula and the temporal pole have also been pointed out by Fulton *et al.* (13).

Decerebration at the midbrain level in dogs, as reported by Anderson *et al.* (14), resulted in a decrease in carbohydrate tolerance which lasted two to three weeks, regardless of whether or not the hypothalamus remained intact. Simple bilateral decortication resulted in no appreciable alteration in carbohydrate tolerance.

HYPOTHALAMUS

The pertinent literature relative to the hypothalamic regulation of visceral functions has been reviewed by Hoff (15, 16). He also discussed the functional relationships of the various groups of hypothalamic nuclei, the hypothalamic influences in the secretory activity of the endocrine glands and in the functioning of the vascular system in different periods of life, and the character of certain hypothalamic syndromes. Harris & de Groot (17) have reported additional experimental data which appear to support the assumption that the secretion of the adrenocorticotrophic hormone is regulated through hypothalamic mechanisms. In a symposium moderated by Hess (18), the major functional connections of the hypothalamus with the cerebral cortex are outlined and discussed in relation to the co-ordination of diencephalic and cortical functions and in relation to organic unity. Hess (19) has also discussed organic order as illustrated by the harmonious functioning

of the sympathetic and the parasympathetic nerves regulated through the diencephalon and the frontal cortex.

Data reported by Simon (20) support the supposition that the increased metabolism associated with encephalography is a result of the sustained stimulation of the centers concerned in the hypothalamus. Faradic stimulation of the rostral portion of the hypothalamus, the pituitary body, or the cervical sympathetic trunk, as reported by Reiss (21), caused an increase in the glucose level in fasting animals. There appears to be located in the rostral portion of the diencephalon a center which is especially important for carbohydrate metabolism. Experimental data reported by Kennedy (22) support the assumption that the hyperphagia exhibited by rats with hypothalamic lesions represents a primitive urge to eat, which is hunger. Under normal conditions, this urge is inhibited by a hypothalamic satiety mechanism which is sensitive to changes in the blood that result from the ingestion of food.

Electrical stimulation of the hypothalamus close to the infundibulum in the female rabbit, as reported by Nowakowski (23), caused ovulation in 85 per cent of the trials. The same stimulation did not cause ovulation after transection of the spinal cord. Ovarian function appears to be impaired following transection of the spinal cord to the extent that the luteinizing hormone does not exert its full effect on the ovary. According to Weidl (24), the existence of a sexual center in the hypothalamus must as yet be regarded as problematic.

In the rat, as reported by Cheng *et al.* (25), section of the hypophyseal stalk does not abolish the adrenal cortical response to an acute stress. The prompt release of the adrenocorticotrophic hormone in the hypophysis, therefore, does not depend on nerve impulses emanating from the hypothalamus. Data reported by Bargmann (26) appear to support the assumption that the hypothalamico-hypophyseal tract serves as a pathway for neurosecretory granules. According to his account, secretory granules which arise in the neurons in the supraoptic nucleus traverse this tract to enter the hypophysis and the third ventricle.

Data reported by Eliasson & Ström (27) support the assumption that the heat-sensitive portion of the hypothalamus coincides with the preoptic middle region, the anterior region, and the dorsomedial and ventromedial nuclei. These data in general corroborate earlier findings of Magoun *et al.* (189). In cats, Ström (28) found that heating of the anterior portion of the hypothalamus caused cutaneous vasodilatation, chiefly in the foot pads. This effect was more marked in the forelimbs than in the hind limbs. In the intestine, vasoconstriction was inconstant. The respiratory rate was increased. In the unanesthetized dog (29), cooling of the hypothalamus when the cutaneous vascular bed was dilated caused constriction of the cutaneous vessels. Under other conditions, cooling of either the rostral or the caudal portion of the hypothalamus resulted in no change in cutaneous blood flow. The magnitude of the dilator response of the cutaneous vessels to heating of the hypothalamus was influenced markedly by changes in the local skin temperature (30).

Electrical stimulation of the rostral portion of the hypothalamus or of the cortex of the frontal cerebral lobe caused cutaneous vasoconstriction in the cat, the dog, and the rabbit. Simultaneous electrical stimulation and heating of the rostral portion of the hypothalamus caused cutaneous vasodilatation. Decortication of the frontal lobe did not abolish the vasomotor effect of either heating or electric stimulation of the hypothalamus. Decerebration at the level of the superior colliculus resulted in diminution of the vascular tonus.

Effective regulation of body temperature in cold environments (5° to $8^{\circ}\text{C}.$) in hamsters, as reported by Brun (31), becomes apparent at ages ranging from 30 to 44 days. This is the age interval in which myelinization in the dorsolateral areas of the caudal portion of the hypothalamus reaches its height. The capacity for thermoregulation, therefore, appears to be related to myelinization in the hypothalamus. These data are in general agreement with data previously reported for albino rats.

From the clinical point of view, as observed by Penfield & Rasmussen (10), impairment of the hypothalamic temperature-regulating mechanisms commonly produces grave autonomic disturbances. Paralysis of temperature regulation due to lesions in the vicinity of the third ventricle results in hyperthermia produced by peripheral vasoconstriction and cessation of perspiration. This is frequently accompanied by hyperpnea and tachycardia.

Brücke (32) pointed out certain important differences in the sympathetic responses to peripheral and to direct hypothalamic stimulation. In a study of the adrenal medullary secretory products, he found no evidence that secretion produced in response to carotid sinus stimulation differs materially from that produced at rest. In either case the output included both epinephrine and norepinephrine.

In experiments reported by De Groot and Harris (33), electrical stimulation of the posterior region of the tuber cinereum or the mammillary bodies in unanesthetized, unrestrained rabbits resulted in lymphopenia comparable in magnitude and time relations to that caused by emotional stress. The lymphopenic response is regarded as the quickest known indicator of pituitary activity (34). Pituitary function, therefore, is influenced from the tuberal and the mammillary regions of the hypothalamus. The interactions of hypothalamic and hormonal influences on gastric, pancreatic, and biliary functions are discussed by Schuetz (35). Chalmers & Lewis (36) have reported data relative to the antidiuretic effects of stimulation of the supra-opticohypophyseal system in man by emotional stress, hypertonic saline, acetylcholine, and nicotine.

MEDULLA OBLONGATA

In an experimental analysis of the central and the chemoreflex components in the respiratory analysis in the dog during acid-base displacements in the blood, Hesser (37) found that metabolic acidosis causes increased activity and metabolic alkalosis causes decreased activity of the respiratory center, and that this center is stimulated directly by increased acidity. The

hydrogen-ion concentration in the center, however, is dependent on the metabolism of the center tissue in only a minor degree. The hyperpnea during acidosis is not markedly altered by elimination of the chemoreflex component, but this component appears to be an essential factor in the finer adjustments of respiration both with respect to carbon dioxide in the arterial blood and arterial oxygen saturation. The response of the chemoreceptors to changes in the hydrogen-ion concentration in the arterial blood appears to be more rapid than that of the central chemoreceptive cells.

By means of localized recording of action potentials in respiratory rhythm and of localized stimulation of the respiratory center in the rabbit, Woldring & Dirken (38) outlined a ventromedial inspiratory portion and a dorsolateral expiratory portion. The inspiratory portion is localized in the reticular formation at the level of the vagus nerve roots. The expiratory portion lies parallel to the tractus solitarius and appears to be connected with the trigeminospinal tract. On the basis of experimental data, Dirken & Woldring (39) concluded that afferent vagus stimulation exerts only an inhibitory effect on the respiratory center.

In experiments on dogs in which the vagus nerve and the cervical portion of the sympathetic trunk on the right side were extirpated, and at least a year later the same operation was carried out on the left side, Braeucker (40) found, after decerebration of these animals, that stimulation of the vagus nuclei elicited typical vagus effects which were abolished by extirpation of the stellate ganglia. These results were explained on the assumption that impulses arising in the vagus nuclei were conducted caudad in the brain stem and the spinal cord and reached the heart and the lungs through the sympathetic trunk ganglia in the third and the fourth thoracic segments.

Central vagal stimulation, as observed by Glass & Boyd (41), is more effective and more uniform than peripheral stimuli in the form of cholinergic or adrenergic drugs for activation of the gastric glands. Glass & Wolf (42) reported data which lend additional support to the theory that the gastric glands are influenced directly through the vagus nerves, but they do not preclude the existence of a hormonal secretory mechanism which involves gastrin.

PERIPHERAL AUTONOMIC NERVES

Independent sympathetic conduction pathways.—Additional data relative to the occurrence of accessory sympathetic ganglia and peripheral sympathetic conduction pathways which are independent of the sympathetic trunk have been reported by Kuntz & Alexander (43) and by Ehrlich & Alexander (44). The anatomic demonstration of such pathways, particularly in the first and the second thoracic segments and in the twelfth thoracic to the third lumbar segments in man, corroborates the physiologic demonstration of residual sympathetic nerve activity in the corresponding dermatomes following sympathetic trunk extirpation. Complete functional sympathetic denervation of any part of the body in which sympathetic conduction pathways which do not traverse the sympathetic trunk are present obviously requires

interruption or blocking of these pathways in addition to those which traverse the sympathetic trunk. On the basis of the distribution of sweating after thoracic and thoracolumbar sympathetic trunk extirpation, Wilson (45) concluded that the only somatic area in which these operative procedures insure complete sympathetic denervation is the leg below the knee.

In a functional analysis of the vasomotor nerves of the hind foot pad in the dog, Randall *et al.* (46, 47) have demonstrated that the major portion of the postganglionic sympathetic fibers concerned are derived from the sympathetic trunk at the sixth lumbar and the first sacral vertebral levels. Most of the preganglionic fibers concerned in the vasomotor innervation of the hind foot pad which make synaptic connections in the sympathetic trunk join it between the fourth and the sixth lumbar vertebral levels. Following degeneration of all the fibers interrupted by extirpation of the entire lumbar portion of the sympathetic trunk, intact vasomotor conduction pathways could be demonstrated by direct faradic stimulation of the tibial and the peroneal nerves. Blocking of these nerves with procaine resulted in prompt vascular relaxation and increased blood flow in the foot. A search for accessory sympathetic ganglia in the dogs used revealed accessory ganglion cells located in relation to the ventral primary rami of the second, third, fourth, and sixth lumbar nerves. The residual sympathetic conduction pathways which remained intact following sympathetic trunk extirpation undoubtedly included synaptic relays in the accessory ganglia.

Afferent conduction from extremities through sympathetic trunks.—With the aid of the cathode ray oscilloscope, Threadgill & Solnitzky (48) have demonstrated the existence in the hind limb of the dog of afferent nerve fibers which traverse the sympathetic trunk. Echlin (49) also reported phantom limb pain elicited by electrical or mechanical stimulation of the lumbar portion of the sympathetic trunk, exposed under local anesthesia, in a patient with an amputated foot. After division of the sympathetic trunk, its stimulation rostral to the section caused intense pain in the limb, but stimulation caudal to the section caused only a mild burning sensation. Extirpation of the lumbar segments of the sympathetic trunk resulted in almost complete relief of the phantom limb pain. In two additional patients, stimulation of the rostral portion of the sympathetic trunk which had been divided rostral to the third lumbar ganglion caused intense pain, but stimulation of the caudal portion failed to cause pain. The pain elicited by stimulation of the sympathetic trunk in these patients obviously was mediated through afferent spinal nerve fibers which traversed the sympathetic trunk. These findings corroborate the earlier experimental demonstration by Kuntz & Saccomanno (188) of afferent conduction from the extremities through the sympathetic trunk in the dog. Additional experimental data which support the assumption that afferent impulses arising in the extremities may be conducted centrally through fibers of spinal ganglion origin which traverse the sympathetic trunk have been reported by Freeman *et al.* (50) and by Kuntz (51).

Vasomotor nerves.—As reported by Franke *et al.* (52), the reflex vasoconstrictor responses in the foot pad of the dog have a latent period 0.5 to 1 sec.

longer than the vasoconstrictor responses to direct faradic stimulation of the sympathetic trunk. Either of these latent periods is several times as long as that of a somatic reflex response. The vasoconstriction may persist 20 to 30 sec. following cessation of the faradic stimulation.

In the cat, as reported by McDowall (53), the blood vessels in the skeletal muscles are less sensitive than other blood vessels to depressor stimulation. They are also less sensitive than those of the skin to changes in internal pressure and may react in the opposite direction.

A depressor reflex elicited by electric stimulation of the distal portion of the vagus nerve has been described by von Euler (54). The afferent impulses concerned appear to be conducted by afferent spinal nerve fibers and to reach the vasomotor center through ascending pathways in the spinal cord. As reported by Fowler (55), vasoconstriction elicited by sympathetic stimulation or by the injection of epinephrine may be accompanied by sludging of the blood within the constricted vessels. This finding may be of practical significance in general surgery, general medicine, and psychosomatic therapy.

Vasoconstriction of the digital vascular bed, as reported by Carmichael (56), may be elicited by either visceral or cutaneous stimulation. The reflex response to minimal cutaneous stimulation is unilateral; the reflex response to stronger cutaneous stimulation is bilateral. The data obtained support the assumption that the vasomotor nerves in the proximal portion of the limb include vasodilator fibers. They also demonstrate the existence of venoconstrictor fibers, but afford no conclusive evidence of the existence of venodilator fibers.

The structure and the functions of chemoreceptors and their distribution has been discussed by De Castro (57). The importance of chemoreceptors in the regulation of respiration is emphasized by Heymans (58). Hypoxia at the carotid chemoreceptors, as observed by Bernthal *et al.* (59), resulted in moderate cardiac retardation. On the basis of their findings, cardiac acceleration due to generalized hypoxia does not appear to be due to stimulation of the carotid chemoreceptors. Vasomotor responses to chemoreceptor stimulation and the mechanism of chemoreceptor stimulation in anoxia have been discussed by Neil (60). Acetylcholine hypertension in atropinized dogs, as observed by Atanackovic & Dalgaard-Mikkelsen (61), appears to be a reflex response to stimulation of the aortic and the carotid sinus chemoreceptors. Data reported by Daly & Schweitzer (62) support the assumptions that stimulation of chemoreceptors results in increased sympathetic tonus, and stimulation of pressoreceptors results in increased parasympathetic tonus.

Data reported by Peterson (63) indicate that certain reflex vasomotor responses in man differ from the corresponding responses in other species. Pathologic states and anesthesia also exert a modifying influence on cardiovascular reactions in man.

On the basis of the regional distribution of blood flow after hemorrhage, Pickering (64) has classified the vascular bed in two broad categories. In the one, which includes the vessels in the extremities, hypoxia does not negate centrally imposed vasoconstriction. In the other, which includes the vascular

bed in the viscera, the brain, and presumably the heart, either hypoxia does not cause vasoconstriction or it is easily reversible. The difference in the vascular reactions in these two categories is less marked following the administration of Dibenamine (N, N-dibenzyl- β -chloroethylamine).

In an extensive investigation of the vasomotor responses to hemorrhage and trauma in dogs, Remington *et al.* (65, 66, 67) found that the lethal bleeding volume was greatly reduced when vasoconstriction after hemorrhage was prevented by the use of Dibenamine, but the animals could survive pressures and flow levels which were fatal to the controls. Sustained vasoconstriction caused by carotid sinus extirpation and vagotomy or by the administration of epinephrine resulted in shortening of the survival time at low pressure and blood flow levels and in reduction in the lethal bleeding volume (65). Dogs subjected to repeated small hemorrhages until death was inevitable exhibited three phases: (a) arterial pressure and cardiac output were decreased, and resistance was slightly increased without significant change in heart rate; (b) the cardiac rate was accelerated, and the decline in arterial pressure and blood flow was temporarily interrupted, but venous pressure was lowered and the cardiac volume was reduced; and (c) compensation gradually failed, and arterial pressure, blood flow, and resistance were further decreased. Resistance and cardiac output appear to be reciprocally related during the early phases of hemorrhage, but not during the late phases (66). The results of trauma of the hind limbs or of the upper abdomen in the dog indicate that vasoconstriction is a significant precipitating factor in traumatic shock. The rises in arterial pressure and in vasomotor resistance of the body are closely related to the onset and the intensity of the trauma. The survival rate after trauma of the limb was greatly increased by partial blocking of the reflex vasoconstriction by Dibenamine in small doses. The animals appeared to become more sensitive to reduction in blood volume as a result of the vasoconstriction caused by the trauma. Consequently the local displacement of fluid into the traumatized areas, where the vessels are dilated, constitutes lethal hemorrhage (67).

The control level of arterial pressure following very rapid transfusion or hemorrhage, as reported by Guyton *et al.* (68), is relatively independent of the blood volume as long as a sufficient quantity is present, but it depends in a large measure on sympathetic activity. In normal animals the readjustment following transfusion at rates used clinically is sufficiently rapid to prevent a significant rise in pressure. After rapid massive hemorrhage the arterial pressure rises somewhat, but complete recovery is slow because interstitial liquid enters the circulation slowly. The arterial pressure differential appears to be dependent on the pressoreceptor-vasomotor mechanisms (69, 70). While these mechanisms are intact, the differential is approximately one-third as great as after complete pressoreceptor denervation. In normal animals, abrupt changes in blood flow into and out of the circulatory system caused oscillations similar to Traube-Hering waves which did not occur following interruption or blocking of the pressoreceptor-vasomotor reflex arcs.

Traube-Hering waves, therefore, appear to be due to pressoreceptor-sympathetic reflex activity.

In a study, with the aid of a preformed tissue chamber, of the vascular reactions in the rabbit's ear to heating of the body, van Dobben-Broekema & Dirken (71, 72) found that the capillaries alone were responsible for the increased temperature of the ear. Neither the arteries, the arterioles, nor the arteriovenous shunts underwent any appreciable changes in caliber. Following sympathetic denervation of the ear, the blood flow through it could still be influenced by raising and lowering the temperature of the blood flowing into aural arteries. Increased responsiveness of the denervated vessels, chiefly the smaller ones, was also demonstrated. The data obtained indicate that the arteriovenous anastomoses function as emergency valves when the balance between the arterial supply and the venous drainage is disturbed. As reported by Girling (73), the critical closing pressure for the blood vessels in the rabbit's ear is increased during constriction due to electrical stimulation.

Following acute occlusion of the femoral artery in young adult human subjects, Shepherd (74) observed that the supply to the foot is increased by indirect heating and by the administration of tetraethylammonium bromide both under resting conditions and in response to exercise. The increased blood flow is made possible by dilatation of the collateral vessels due to the release of the sympathetic vasomotor tonus.

In experiments on dogs reported by Ederstrom (75), hyperthermia resulted in shunting of the blood to the heat-dissipating area provided by the tongue and away from the skin. In this nonsweating animal, superheating of the body results in a redistribution of the blood, the direction of which is the reverse of that which occurs in man. Section of the spinal cord in the dog was followed by lowering of the arterial pressure and increased flows of blood in the hind foot pad and the intestine. Hyperthermia after spinal cord section further increased the fall in arterial pressure; the flow of blood in the hind foot pad and the intestine also fell below the control levels. The flow of blood in the tongue was relatively unaltered, whereas in the normal animal hyperthermia caused a marked increase in the blood flow in the tongue.

In the human hand, as reported by Kerslake & Cooper (76), the time of onset of vasodilatation in response to heating of the trunk or the leg in a radiant heat cradle showed a latent period of 10 to 15 sec., irrespective of the rate of heating. Since the response in the hand to heating of the leg alone was unaltered by a thigh cuff inflated to 200 mm. Hg, it was concluded that the vasodilatation in the hand was brought about reflexly by afferent impulses which arose in the heated skin of the leg. As observed by Löhr (77), heating of the trunk does not elicit reflex vasodilatation in the hand following complete sympathetic denervation of the upper extremity. Reflex vasomotor responses to thermal cutaneous stimulation are also abolished in the dog following sympathetic denervation (78).

In patients with high transverse lesions of the spinal cord, as reported

by Goetz & Ames (79), immersion of the feet in warm water results in vasodilatation in the upper extremities. Occlusion of the circulation in the immersed extremities abolished this response. The vasodilator response, therefore, appears to be dependent on the return of heated blood to the thermosensitive center in the hypothalamus. Heating of an occluded limb, according to their account, results in a marked rise in arterial pressure due to the accumulation of metabolites in the muscle. The recognition of this hormonal mechanism associated with reflex heating is regarded as clinically important. This interpretation appears to be diametrically opposed to that of Kerslake & Cooper.

The effects of changes in posture on the peripheral circulation have been discussed by Goetz (80) in relation to the comparative results of sympathectomy in the extremities and in relation to indications for sympathectomy in patients with marked wasting of muscles. His data appear to support the assumption that the venous limb of the vascular bed plays a role in peripheral circulation which has not been generally recognized. Glaser *et al.* (81) have reported data which appear to support the supposition that in normal young human subjects the liver and the lungs contain more blood when the body is exposed to low ambient temperature than when its environment is warm.

Effective concentrations of either epinephrine or norepinephrine applied to the bats wings, as reported by Nicoll (82), always caused constriction of the arteries and the arterioles and never dilatation. In vessels such as the terminal arterioles, the precapillary sphincters, and the venules, which normally exhibit rhythmic activity, the constriction phase was increased by the administration of either substance. Pratt & Burdick (83) have reported experimental data which appear to support the assumption that epinephrine acts directly on the circulation through the liver to shunt the blood away from the parenchymal cells.

In cats, following extirpation of the superior cervical sympathetic ganglion in some and preganglionic cervical sympathectomy in others, Kirgis (84) found that the radial muscles of the iris were somewhat more sensitive to epinephrine following sympathetic denervation by ganglionectomy than by section of the preganglionic fibers. The degree of sensitivity to epinephrine remained about the same 48 months after sympathetic denervation as it was earlier in the postoperative period. Following functional regeneration, the control pupil reacted more strongly to epinephrine than the sympathectomized one.

Data reported by Hiatt (85) demonstrate antagonizing effects of quinine and quinidine on the pressor reactions elicited by epinephrine and splanchnic nerve stimulation in the dog. These findings confirm data reported earlier. Variations in the antagonistic effects of certain sympatholytic substances, including Priscoline (benzazoline) and yohimbine, on the pressor effects of epinephrine and norepinephrine in the rat have been reported by Gross & Stricker (86). As reported by Konzett (87), epinephrine and norepinephrine generally augment the response of acetylcholine administered

immediately afterward both in normally innervated and denervated, isolated perfused superior cervical sympathetic ganglia in the rat. The augmenting effect is not influenced by Dibenamine or by the alkaloids of ergot. The ganglion cells in the superior cervical sympathetic ganglion appear to be provided with receptors for epinephrine and related substances.

Malméjac *et al.* (88) have reported data relative to the effect of splanchnic stimulation on the output of epinephrine. Hermann *et al.* (89) have discussed the influence of muscular exertion on epinephrine's inhibitory action on the intestinal musculature. Additional data relative to the peripheral vasoconstrictor action of tetraethylammonium bromide have been reported by Jourdan & Chatonnet (90).

A highly active pressor substance which produces a prolonged effect in rats has been obtained in fairly pure form by Schroeder & Olsen (91) from the arterial blood of hypertensive patients. It was present in the blood of patients with hypertension of either neurogenic or renal origin, but only in small quantities in the blood of patients with essential hypertension, and rarely in normotensive patients. It is a dialyzable, nonprotein substance containing an amino group which is essential for its activity (92).

Freyburger *et al.* (93) have reported the results of experiments in which stimulation of the spinal cord caused an increase in arterial pressure which could be blocked by tetraethylammonium in the cat and the monkey but not in the dog and the rabbit. As reported by Prochnik *et al.* (94), the pressor response to bilateral occlusion of the carotid arteries in anesthetized dogs is directly related to the pre-existing mean arterial pressure. Additional data relative to neurochemical regulation of arterial pressure have been reported by de Molina *et al.* (95).

In a study of the effects of sympathectomy on the blood flow in the hand, Barcroft & Walker (96) measured the flow in 14 sympathectomized hands daily for a period of approximately two weeks. In five hands with normal blood vessels the average postoperative flow was 46 cc. per 100 cc. of hand per min. One week after operation it decreased to 11 cc., and two weeks after operation to 6 cc. per 100 cc. of hand per min. In the other nine hands, in which the blood vessels had undergone pathologic changes, the average blood flow was 20 cc. per 100 cc. of hand per min. immediately after operation. After the first postoperative week it was 7 cc., and after the second week it was 3 cc. per 100 cc. of hand per min. Recovery of tonus in the arteries, the arteriovenous shunts, and the capillaries took place at approximately the same rate after both ganglionectomy and preganglionic sympathectomy.

As reported by Stein *et al.* (97), the sensitization of the blood vessels in the muscles of the leg in man following sympathectomy is more marked for the vasodilator than for the vasoconstrictor mechanism. They regard this as a possible factor in the clinical improvement following sympathectomy in some patients with claudication. Sensitization in the cutaneous vessels appears to be too inconsistent to be clinically significant.

In dogs with unilateral lumbar sympathectomy, as reported by Deterling & Essex (98), the administration of epinephrine immediately after the oper-

ation caused a brief rise in arterial pressure and outflow in the femoral veins coincident with the onset of the rise in arterial pressure. This effect was only less marked in the sympathectomized hind limb than in the normally innervated one. The circulation through the kidneys exhibited comparable alterations. The blood vessels, therefore, may exhibit hypersensitivity immediately after either ganglionectomy or preganglionic sympathetic denervation. Inhibitory action of epinephrine at parasympathetic synapses has been reported by Tum Suden & Marazzi (99). This appears to be a general phenomenon at cholinergic synapses.

Localized trophic changes in the skin and the subcutaneous tissue associated with local infections have been studied by Wunche (100). These phenomena possess diagnostic value since the cutaneous manifestations are localized in the dermatomes corresponding to the segments in which the infection is located. The trophic changes appear to be caused reflexly by stimulation at the site of the infection.

In young dogs, as observed by Gullickson *et al.* (101), prolonged chronic sympathetic stimulation (23 to 70 days), by the use of implanted electrodes, resulted in retardation of the growth of the long bones of the limb. Sympathetic denervation of a limb resulted in slight acceleration of the growth in length of the long bones.

Additional experimental data which support the assumption that the blood vessels of the liver are innervated through sympathetic nerves but are devoid of parasympathetic innervation have been advanced by Senevirante (102). The facility with which these vessels react to sympathetic stimulation may be a factor in the pathogenesis of diseases of the liver.

With the aid of a method by which the vasodilator afterreaction can be estimated quantitatively, Wolff & Pochin (103) found that this reaction increases as the cooling temperature is lowered and as the cooling period is lengthened up to 1½ hr., due to the release of a chemical substance caused by injury to the tissues. Although the blood flow in the extremities at low ambient temperatures is influenced by the autonomic regulation of the vascular system, it is determined by the thermal state of the body as a whole (104).

Data reported by Shaw *et al.* (105) appear to support the assumption that sympathetic vasodilator neurons differ inherently from vasoconstrictor neurons. The former appear to be less susceptible than the latter to nicotine, lobeline, yohimbine, and tetraethylammonium chloride, and more susceptible to acetylcholine and quinine methiodide. Data reported by Burn (106) support the assumption that there exists a secondary hemostatic mechanism which exerts its influence chiefly on the cutaneous vessels. Capillary filtration appears to be increased during sympathetic stimulation (107). The excretion of dye through a synovial membrane following sympathectomy probably is influenced only by the changes induced in the capillary circulation (108). In the cat, as reported by Peart (109), stimulation of splenic nerves caused the appearance in the plasma of an active substance which appeared to be chiefly norepinephrine. On the basis of clinical data, Thalhammer & Janicek (110) support the hypothesis that the autonomic nerves exert a significant influ-

ence on the numbers and the distribution of leukocytes in the circulating blood. Kwerch & Leibetseder (111) reported an increase in the leukocytes in the peripheral blood and of megakaryocytes in the bone marrow due to sympathetic paralysis by the administration of dihydroergotamin. Vagus paralysis by the administration of atropine resulted in only a slight increase in the number of leukocytes, but in a marked decrease in the number of erythrocytes in the peripheral blood. In normal and sympathectomized dogs made anemic by frequent bleeding, Orahovats & Root (112) found that the rate of hemoglobin production was slightly less in the sympathectomized than in the normal animals.

An extensive review of the literature bearing on the role of the autonomic nerves in allergic disease has been prepared by Williams (113). He also advanced a concept of allergy as autonomic dysfunction which he regards as more consistent with clinical data than the antigen-antibody concept. It also affords a better working hypothesis for both diagnosis and treatment (114).

Enteric neurons.—Data which appear to support the assumption that the myenteric ganglia include ganglion cells of two functionally distinct types have been advanced by Ambache (115). Stimulation of those of the one type, which are cholinergic, causes contraction and stimulation of those of the other type, which are adrenergic, causes inhibition of the gastrointestinal muscles.

Vagus nerves.—Vagotomy in the treatment of patients with peptic ulcer, as reported by Kirsner *et al.* (116), resulted in no appreciable changes in the gastroscopic or the histologic picture of the gastric mucosa. In ulcer patients with complete vagotomy, Woodward *et al.* (117) found gastric acid secretion reduced to a level below normal. Following complete vagotomy in dogs, they observed no increase in gastric secretion in response to sham feeding or to insulin hypoglycemia. Following isolation of the stomach with the vagus nerves intact in the dog, section of one vagus nerve in the neck resulted in no alteration in the volume or the acidity of the gastric secretion. Bilateral vagus resection plus extirpation of the pyloric antrum in dogs, as observed by Oliver (118), adequately suppresses gastric secretory activity and results in the degree of anacidity necessary to prevent stomal ulcer which usually follows gastrojejunostomy and diversion of the duodenal secretions, bile, and pancreatic juice into the terminal portion of the ileum. Glass *et al.* (119) reported a marked increase in the concentration of the mucoproteose fraction of mucin and a marked decrease in the output of glandular mucoprotein in man following vagotomy and subtotal gastric resection.

Two years after complete bilateral vagotomy in dogs, Deaton *et al.* (120) found that gastric motility, as indicated by fluoroscopic examination, was normal; but some animals exhibited marked pylorospasm and retardation of gastric emptying. The gastric secretory response to local stimulation was subnormal. Critical evidence that gastrin is not released in dogs by vagus stimulation has been advanced by Janowitz & Hollander (121).

In studies on the stimulating mechanism of gastric secretion, Linde (122)

obtained data which support the assumptions that the peptic cells are stimulated directly by acetylcholine liberated by vagus stimulation and that histamine plays a role in the cephalic phase of gastric secretion. Gastrin appears to exert an effect by the release of histamine. Synergic co-operation between the vagus secretory and the pyloric hormonal mechanism, therefore, appears to be indicated. As observed by Lim & Mozer (123), the amount of gastrin liberated due to vagus stimulation is very small.

Faik *et al.* (124) reported a delay of approximately 15 hr. in gastric emptying in the dog following bilateral vagotomy. The intestinal activity normally elicited by the sight and the smell of food was abolished. The feeding reflex was delayed and shortened in duration. The peristaltic waves were reduced in frequency and in duration, particularly in the ileum. As reported by Sloan (125), strong faradic stimulation of the vagus nerve at the root of the lung in the dog during adequate ventilation had no appreciable effect on the heart rate, but the same stimulation during hypoxia or asphyxia resulted in cardiac inhibition and frequently in cardiac arrest. Vagus reflexes during intrathoracic operations, as suggested by the data advanced, may be unimportant while the oxygen supply is adequate, but they may become dangerous when the oxygen supply is deficient.

In patients with inoperable bronchial carcinoma, as reported by Klassen *et al.* (126), unilateral vagotomy below the origin of the recurrent nerve abolished the cough reflex on that side and, in most of the patients, the pain of bronchial origin. This suggests the mediation of pain through vagus afferent fibers, which is contrary to current concepts of vagus afferent function. Bronchospasm was not abolished by bilateral vagotomy, the respiratory movements of the bronchi were not altered, and tracheobronchial clearance of lipiodol was not impaired.

Data reported by Shafer & Kittle (127) support the assumption that sympathetic hyperactivity may result in gastric secretory changes comparable to those caused by vagotomy but less marked. Since sympathetic denervation of the stomach results in increased gastric secretory activity and increased total gastric acidity and peptic activity, it is suggested that sympathetic nerve activity normally inhibits gastric secretion.

Extirpation of the celiac and the superior and inferior mesenteric ganglia in dogs, as reported by Lillehei (128), regularly resulted in fulminating diarrhea associated with bloody stools with increased amounts of mucus, and frequently in peptic ulceration in the stomach and the duodenum. When vagotomy was carried out simultaneously with extirpation of the celiac and the mesenteric ganglia, peptic ulcers and gastroenteritis failed to develop.

Distention of the esophagus in human subjects following sympathectomy, as observed by Williams (129), gave rise to sensations. In the absence of sympathetic nerves along which afferent spinal nerve fibers could reach the esophagus, it was concluded that the impulses in question were conducted through afferent vagus fibers. This is not in agreement with current conceptions of sensory conduction from visceral organs.

Bozler & Burch report (130) corroborating an earlier finding of Gesell & Hamilton (190) that afferent impulses of pulmonary origin conducted through the vagus nerves are predominantly excitatory and exert a continuous influence on respiration. The afferent vagus fibers concerned with respiratory reflexes, according to Wyss & Rivkine (131), fall into three categories, but those in each category are not related to distinct groups of pulmonary receptors.

Data reported by Middleton *et al.* (132) appear to support the assumption that the cardiodepressor effects of vagus stimulation are mediated chiefly through B fibers, with the participation of some delta fibers. They also corroborate the finding of certain other investigators that cardiomotor fibers make up only a minor portion of the total fiber content of the vagus nerve.

Using the dog as the experimental animal, Ederstrom (133) found that the interval of cardiac arrest due to stimulation of the distal portion of the divided vagus nerve was decreased during a rise in body temperature from several seconds at normal temperature to a fraction of a second when the rectal temperature was 45°C. The systolic arterial pressure was only slightly decreased at high temperatures.

Visceral reflexes.—In experiments reported by Richins (134), the pancreas of the cat was rapidly frozen *in situ* after section of the splanchnic nerves and faradic stimulation of the celiac ganglia. Sections of the pancreas prepared by the rapid freezing-drying technique, showed the arterioles well filled and the corresponding veins engorged with blood. The engorgement of the capillaries was even greater when the adrenergic nerves were blocked with ergotamine, but the capillary bed was relatively ischemic when the cholinergic nerves were blocked with atropine. During blocking with atropine, the blood appeared to flow through the arteriovenous shunts, most of which are located in interlobular septa. Complete capillary ischemia of the pancreas could be elicited reflexly by distention of a segment of the small intestine. Such ischemia probably exists only during stimulation which results in the opening of many arteriovenous shunts. Hurlimann & Bucher (135) have reported data which show that the arteriovenous shunts in the rabbit's ear vary in caliber, but all are constricted by epinephrine in approximately the same degree. They appear to be more responsive to epinephrine than are the arterioles and the capillaries.

Bock *et al.* (136) have reported the results of experiments in which faradic stimulation of the renal nerves resulted in vasoconstriction in the kidney sufficient to cause cessation of the blood flow for a few minutes, which was followed by rapid recovery. The renal cortex exhibited marked blanching while the medulla remained pink, but vascular shunts could not be demonstrated. Houck (137) also failed to observe shunting of blood from the renal cortex in the dog due to renal nerve stimulation.

Electrical stimulation of sufficient intensity to give rise to pain, applied to the tooth pulp in curarized rabbits and anesthetized and unanesthetized cats, according to Goetzl & Bien (138), caused a fall in arterial pressure in the anesthetized animals and a rise in arterial pressure in the unanesthetized

ones. Painful electrical stimuli at 5-sec. intervals, as reported by Van Liere *et al.* (139), caused inhibition of intestinal motility in albino rats, but had no appreciable effect on intestinal motility in hooded rats. It is suggested that the hooded rat may be less sensitive to pain than the albino due to its closer genetic relationship to the wild rat in which alertness is essential to survival. Additional experimental data relative to the myenteric reflex in dogs have been reported by Thomas (140). Excision of the outer layers of the colon, including the myenteric plexus, from a zone 1 to 6 cm. in length and 6 to 8 cm. proximal to the pelvic peritoneal reflection, as reported by Klinge (141), resulted in no appreciable alterations in the size and the frequency of stools.

During intrathoracic operations Niedner (142) observed more or less definite patterns of atelectasis. The configuration of these patterns suggests the neurogenic character of the respiratory reactions and indicates active participation of the lungs in respiration. Reeve *et al.* (143) have pointed out that inhibitory respiratory reflexes which may occur during abdominal surgery may be caused by pressure, tension, or friction on the parietal peritoneum and the diaphragm. Such reflexes may be abolished by local anesthesia of the peritoneum, since the afferent limbs of the reflex arcs involved traverse intercostal nerves. Aviado *et al.* (144) reported respiratory and circulatory reflexes in the dog elicited by impulses arising in pressoreceptors due to increasing pressure in the perfused right side of the heart and in the pulmonary blood vessels.

Reflex vascular reactions in the corpora cavernosa penis which are associated with peritonitis have been described by Golla (145). They appear to be reflex responses to stimuli arising in the peritoneum which are mediated through the lumbar sympathetic reflex center. A trigeminal-cardiac reflex which may be used as a functional test of the reactivity of the heart to extracardiac stimulation has been described by Brauch (146). It may also be a factor in anginal attacks precipitated by cooling of the face.

Experimental data obtained by the use of tetraethylammonium as a blocking agent, reported by Pardo *et al.* (147), appear to support the assumption that there exist certain efferent conduction pathways to the heart which either include no synaptic relay or which include a synapse which is invulnerable to this blocking agent. Lockett (148) has reported a method for measuring the changes in heart rate and systolic arterial pressure caused in unanesthetized atropinized dogs by certain sympatheticomimetic amines.

Pollock *et al.* (149) have pointed out that injuries of the spinal cord may result in defective autonomic regulation due to interruption of direct and reflex suprasegmental conduction pathways. Failure of impulses of central origin, which normally inhibit heat production, to reach the periphery may result in hyperpyrexia in the presence of high ambient temperature. Likewise blocking of suprasegmental inhibitory impulses may result in excessive reflex sweating and vascular hypertonus.

Experimental data reported by Langley & Whiteside (150) appear to support the assumption that in the dog the capacity of the urinary bladder to accommodate to varying volumes of liquid content is inherent in the de-

trusor muscle. In the absence of its parasympathetic innervation the bladder becomes markedly hypertonic. This phenomenon cannot be explained on the basis of available data. The sympathetic nerves apparently play no significant part in the mechanism of accommodation or in the tonus of the urinary bladder.

On the basis of observations based on 300 bladder fluoroscopies, Muellner (151) has pointed out that man's ability to start or to stop the flow of urine depends in a large measure on the normal functioning of the muscles of the pelvic floor, the abdominal wall, and the diaphragm.

Innervation of sweat glands.—Local responses of sweat glands to intradermal injection of adrenergic stimulating agents have been found by Wada (152) and Haimovici (153, 154). Data reported by Sonnenschein *et al.* (155, 156) support the assumption that the sweat glands of the forearm may be stimulated directly by epinephrine and other adrenergic stimulating agents, but they do not prove the existence of adrenergic nerve fibers to sweat glands. Patton (157) concluded, on the basis of experimental data, that in the cat sweat glands in the pawpads are innervated exclusively through cholinergic fibers.

As observed by Randall & McClure (158), individual sweat glands discharge periodically. The initial sudomotor response to mild exercise or increased ambient temperature is an increase in the number of secreting glands. If the requirements of temperature control are not adequately met by this response, further heat elimination may be brought about by an increased output of the individual glands.

The relationship between blood flow, skin temperature, evaporation rate, and sweating, as observed by Randall & Hertzman (159), vary in different cutaneous areas. On the volar surfaces of the hands and the feet the sweating rates are adequate to provide for evaporative heat loss in excess of the heat delivered by the blood. In the face the sweating rates are low although the blood flow is relatively high. The cutaneous areas which exhibit maximal blood flow and sweating rates which are intermediate include the major portion of the body surface. Calculations based on the assumption that all the sweat is vaporized indicate a marked initial thermal deficit in the cutaneous blood flow which decreases rapidly to a level at which an appropriate caloric balance may be established.

In young men exposed to successively higher ambient temperatures, as observed by Randall *et al.* (160), sweating appears first on the calf and the thigh, then on the lower trunk and lastly on the upper extremities and the forehead. During exposure to relatively high environmental temperatures, Ederstrom *et al.* (161) found evaporative heat losses to be particularly great from the leg, the trunk, and the forehead.

Issekutz *et al.* (162) have pointed out that sensations of heat do not parallel sweating caused by local heating. They infer that reflex sweating is elicited through afferent neural pathways other than those which mediate sensations of heat. The former probably comprise fibers of smaller caliber than the latter. Sudomotor reflexes involving discharges from individual sweat pores

have been described by Ebbecke (163). Reflex sweating due to pressure on the body surface has been reported by Takagi & Sakurai (164).

Areas of low electrical resistance in dermatomes corresponding to the segmental innervation of a diseased viscus have been observed by Korr (165, 166). Postural and myofascial disturbances in human subjects may also induce and maintain perspiration and other sympathetic activity in the corresponding cutaneous areas. If areas of referred pain are present, the cutaneous areas which exhibit exaggerated sympathetic activity coincide with the painful areas.

Data obtained by Roth & Craig (167), who carried out sweating tests on 1,022 patients within eight to fourteen days after sympathectomy and later, warrant the conclusion that sympathetic denervation was incomplete in a high percentage of the patients. In some patients the areas of anhidrosis were somewhat less extensive five to six months later than immediately after sympathectomy. After the first five or six months following operation the patterns of sweating remained fairly constant during the follow-up period which for some of the patients extended over 16 years. Data relative to the sensitization of the sweat glands in the pawpads of the cat following sympathetic ganglionectomy and following preganglionic ramisection have been reported by Simeone *et al.* (168).

Abolition of the skin temperature gradient or of sweating alone cannot be regarded as conclusive proof of complete sympathetic denervation or of complete sympathetic nerve blocking. As observed by Hoobler *et al.* (169), the blood flow returned to the preoperative level in three to seven days after sympathectomy in most of the patients studied. In some patients it continued at this level for periods up to 15 months despite continued anhidrosis and elevated digital skin temperature.

Data reported by Palumbo *et al.* (170) and Randall *et al.* (47) support the assumption that sudomotor activity in a sympathectomized area is mediated through sympathetic conduction pathways which are not interrupted by sympathetic trunk extirpation. Löfgren (171) has attempted to explain sudomotor activity in a sympathectomized area on the basis of regeneration of sympathetic conduction pathways.

A skin galvanometer which gives a graphic record of sympathetic nerve activity indirectly through changes in the electric resistance of the skin has been described by Richter & Whelan (172). The term, "sympathetic dermatome," to designate the cutaneous area of distribution of sympathetic fibers derived from a given segment of the sympathetic trunk has been proposed by Mentha (173). He has pointed out that knowledge of the sympathetic dermatomes may be utilized in the interpretation of sympathetic anomalies and that elevated temperature may exist in a sympathectomized area in the presence of only slight vasodilatation.

Data relative to the levels of outflow of the preganglionic fibers concerned with sudomotor activity in various cutaneous areas, obtained by the use of skin resistance patterns following sympathectomy, have been reported

by Thompson *et al.* (174). These data corroborate the conclusion that the skin resistance pattern does not in all cases afford an exact indication of the extent of the sympathetic denervation. Data obtained by Ratcliffe & Jepson (175), by the use of a new technique for the measurement of skin resistance, indicate that complete surgical sympathetic denervation of the thigh requires removal of the highest lumbar sympathetic trunk ganglion. Van Metre (176) has pointed out that low electric skin resistance in a painful area indicates sympathetic nerve activity in that area. As observed by Hardy & Furer (177), the magnitude of the change in skin resistance caused by induced pain increases with the intensity of the pain. The response to pain is increased by anxiety, but adaptation usually takes place rapidly. Registration of electrical skin resistance, as observed by van der Valk & Groen (178), may be used as a measure of emotional stress in persons who exhibit no apparent evidence of emotional excitation. Ruf & Müller (179) have reported data which appear to support the assumption that electrical skin resistance affords a useful criterion of the functional balance of the autonomic nerves. As reported by Schölmerich & Hildebrandt (180), the response of the sweat glands to local heating may be modified by disturbances of the sudomotor nerves. They explain rhythmic changes in the output of the sweat glands on the basis of rhythmic changes in the blood flow in the cutaneous vessels. The intensity of water elimination is also correlated with the thermal sensitivity of the skin. A theory of reflex control of body temperature at rest and during exercise by utilization of vasomotor adjustments and sweating has been proposed by Bazett (181).

Innervation of the eye.—Pupillary dilatation in response to sympathetic nerve stimulation, as observed by Berteau & Jones (182), does not depend on vascular changes in the eye. In experiments on dogs, the pupil dilated in response to preganglionic stimulation of the superior cervical sympathetic ganglion 45 to 60 min. after elimination of the blood supply to the eye. After sympathetic denervation of one eye, equal stimulation of the oculomotor nerves may elicit a stronger pupilloconstrictor response in the sympathetomized eye than in the normally innervated one, due to disinhibition of the parasympathetic nerves. The extent of the reflex pupillary dilatation in an experimental animal, as reported by Lowenstein & Lowenfeld (183, 184), appears to be determined by the stimulus, the level of illumination, and the emotional state of the animal. The dynamic pattern of the reflex response of the pupil to light is determined by the strength, the duration, and the timing of coincident sympathetic and parasympathetic nerves. The sympathetic nerves may exert an influence on its dynamic pattern. Additional data relative to the functions of the ciliary muscles in accommodation have been reported by Pau (185). Data relative to the role of the sympathetic and the parasympathetic nerves in the regulation of intraocular tension have been advanced by Schmerl & Steinberg (186) and Dawson & Matchett (187).

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HEARING

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This review of the research and studies of the function of hearing covers the period from approximately July, 1948 to June, 1951. Three years have elapsed since this topic was reviewed in this publication by Walzl (1). It is very difficult to draw a sharp borderline between the psychology and physiology of hearing, but since the field of hearing in the meantime, has been reviewed by Newman (2) in the *Annual Review of Psychology*, an attempt has been made to limit the scope of the present chapter to more physiological aspects of the sensory process in the ear. This has been done because there is ample material within the subject to fill the space allotted for this chapter. Some papers have been summarized, not because they contain important new data, but for the reason that they present unaccepted opinions or revive abandoned views, and so serve to give the reader a total picture, not only of current work, but of current thought about the field of hearing. Some articles which are essentially clinical contain valuable physiological data and, therefore have been included. The historical development of theories of hearing has been described by Békésy & Rosenblith (3) and in a chapter by Hirsh (4) the historical background of binaural interaction has been treated. A book by Kosteljik (5) also presents the experiments and theories devised to explain the phenomena of hearing.

In his book entitled *Theory of Hearing*, Wever (6), one of the pioneer investigators in this field, has given an authoritative review. He develops a new theory, the "volley theory," which combines the virtues of the two previous major theories, those of "place" and of "frequency," and discusses it in the light of physical, physiological, and clinical evidence.

TRANSMISSION ROUTES TO THE INNER EAR

One of the fundamental difficulties in the understanding of hearing has been the lack of knowledge of the physical characteristics of the aural structure. Owing to the introduction of new techniques for physical measurements upon the various components of the conduction apparatus, our knowledge of the transformer properties is now expanding.

Middle ear.—The vibrations of various parts of the tympanic membrane in response to sound stimulation of different frequencies (7,8) and the adjusting function of the tensor tympani in sound transmission have been studied (9). The physical behaviour of the collagen fibers and the elastic fibers which form membranes, ligaments, tendons, and articulations in the ear has been investigated by Kobrak (10). Besides these direct observations, Wever, Lawrence & Smith (11) have extended their experiments on the conductive system of the ear by using the cochlear response in order to

study the efficiency of sound reception as affected by lowering the air pressure in the middle ear. The increased stiffness and damping of especially the ear drum to changes of air pressure is, particularly for the low and middle frequencies (12, 13), reflected by a marked drop in the microphonic output. Rudmose *et al.* (14) measured the threshold of hearing for 15 ears in a decompression chamber at ambient pressures corresponding to altitudes of 35,000 ft. and sea level. The final corrected results showed that the shift in the average threshold was within ± 2.5 db.

In view of the significance of the middle ear problem in both military and commercial aviation, a paper by Chang and his associates (15) is of interest. They studied quantitatively the pressure changes and barotrauma in the middle ear resulting from decompression and recompression and made detailed observations on the function of the Eustachian tube. The same subject has been treated in part by Riecker (16). The role of the mastoid cells as a sound-absorbing system for pent-up sound waves and the effect of this mechanism of facilitating the free movement of the tympanic membrane has been discussed by MacDonald (17).

Békésy (18) describes a method for the post-mortem measurement of the conductive loss in the middle ear. By subtracting the value for conductive deafness from a previously taken audiogram showing the over-all deafness, he got the percentages of hearing loss due to conductive deafness and nerve deafness. For the purpose of observing the mobility of the stapes *in vivo*, he constructed an optical instrument similar to a cystoscope but with a diameter less than 2 mm. and with external illumination. This endoscope could be introduced into the tympanic cavity.

Several new papers deal with the function of the round window and with the effect of differential mobility of the windows of the cochlea on the mechanism of hearing (19, 20). The idea of improving the hearing of patients by surgical blocking of the round window with the introduction of grafts into the niche has very little support in the light of old and new experimental findings (21).

Renewed attention has been directed to the round window as an alternative route of entrance of vibrations into the inner ear (22). This is a question which has been debated for many centuries. The majority of the investigators in this field consider the round window only as a compensatory opening for vibrating fluid column of the cochlea and assume that, under normal conditions, this window is of no importance for sound conduction to the inner ear (23). Popper (24), however, supports the view that the round window is part of the sound pathway. At the present state of our knowledge, many basic questions remain to be answered, pertaining, for instance, to the normal and optimal tension of the membrane and to an elementary quantity such as its thickness, before we can get a complete and satisfactory explanation of the function of the round window membrane.

Some experimental data on the physical properties of the round window membrane and the oscillations of the incus in response to round window

and ossicular sound conduction have been furnished by Kobrak (25). He found that the vibrations of the incus are about equal in ossicular and fenestral (sound entering the cochlea through the round window membrane) conduction. Wever, Lawrence & Smith (26) measured the cochlear response to sound stimuli introduced through a tube sealed over the oval or round window after the middle ear structure was removed. They found that sound is almost as effective in producing electrical potentials when applied to the round window as when applied to the oval window. Sound entering by way of the oval window was in general slightly favoured, but the difference never exceeded 4 db. Complete removal of the ossicular chain, except for the footplate of the stapes, resulted in serious loss of sensitivity for all tones. This loss was greatest for the middle frequencies and somewhat less for the low and high frequencies. The over-all average loss was 28 db. They calculated the contribution to sensitivity that an ideal transformer action should give and obtained a value of 30 db.

The characteristics of the middle ear apparatus have been investigated in terms of the cochlear potentials by Wever & Lawrence. First, they showed how the drum, the two outer ossicles, and their suspensory system fulfill the duties of a mechanical transformer with only slight disturbance of the response pattern (27), and in a later paper, by a somewhat different method, they were able to extend the discussion to the third ossicle, the stapes (28).

In a most interesting and detailed investigation by Békésy (29), the structure of the middle ear and the hearing of especially one's own voice by bone conduction have been studied. In this necessarily brief review, it is hard to make a selection among the author's several important points. The form and tension of the tympanic membrane were studied in man and different animals. In man, the ear drum is stiffened and is like a piston, but does not make piston-like translational movements. The movement is a rotation in an axis above and tangent to the upper rim of the ear drum. The loading of the drum with the handle of the hammer eliminates resonance peaks and improves the sensitivity and frequency range of air-borne sounds. The head of the hammer is required in order that the centres of gravity and rotation of the hammer should be at the same point. The construction of the ossicle chain prevents untoward movements in vibration.

Onchi (30) summarized our knowledge about the anatomy and physiology of the ear, translated it into physical terms, and deduced formulae showing the mechanics of the middle ear through the Lagrangian equation.

Bone conduction.—The otologists are aware of the fact that potentially there may be considerably more cochlear effect than is apparent by ordinary bone conduction tests, or otherwise bone conduction hearing and cochlear nerve function cannot be synonymous. This is a matter of common occurrence and, of course, particularly disturbing when trying to evaluate the effect of an operation aimed at improving auditory sensitivity. It must be the aim of clinical bone conduction measurements to eliminate the influence

of all factors distal to the end organ or else to account for the effect of their variation. The physiology of bone conduction has, however, made advances through new methods of measurement which eliminate the variable influences of different factors. The problem has been studied both from a clinical (31 to 36) and theoretical point of view (37, 38).

MacDonald (39), using a new special bone conductor, showed how latent cochlear function varies according to the structure of the mastoid bone. He, however, disregarded the absorption of sound by the skin and subcutaneous tissue. The older findings by Alexander that loudness perception, as estimated by bone conduction, may be different in air conduction has been reinvestigated by Zwislocki (40). Experiments showed this behaviour to be the same, provided that in both cases the sound is heard either binaurally or exclusively monaurally (41). His results are discussed in regard to summation (42) and head vibrations (43) and, once again, it is pointed out that to ensure monaural hearing by bone conduction, the ear not under investigation has to be masked by means of a noise (44).

Békésy (29) has measured the smallest amount of energy able to produce a sensation and gave a value of 0.2 to 0.5 erg for the smallest energy of impact on the teeth that can be heard by bone conduction. That the mode of vibration of the head is of significance for bone conduction has long been understood. Békésy (43) has again turned to this problem and this time measured the pattern of the head vibrations and the velocity of the deformation waves traveling along the bony wall of the skull.

COCHLEAR MECHANICS

A translation into English of earlier articles (45, 46) by Békésy on the physical properties of the cochlear partition in anatomical preparations and in models of the inner ear has been recently published in the *Journal of the Acoustical Society of America*. In these papers, the reader can find a wealth of stimulating results and ideas. They have also been reviewed in a paper by Perlman (47) which is essentially a summary of the work of Békésy and is useful for its references.

Békésy found a definite frequency distribution along the basilar membrane for frequencies between 25 and 2,000 c.p.s. Direct measurements with his superior technique of some physical phenomena taking place in the cochlea led him to the conclusion that the influence of the dimensions of the cochlear canal is of little importance on the vibration-mechanism of the inner ear. The pattern of vibration of the cochlear partition is determined primarily by the volume elasticity of the membrane and of the fluid in the immediate vicinity of the eddy.

In contrast to many earlier theories of hearing based on hypothetical suppositions, we now have the experimental data previously obtained by Békésy; they have been used for the numerical solutions of new theories and have proved to be adequate to give a numerical proof for essential assumptions and simplifications needed in the mathematical analysis. Peter-

son & Bogert (48) have presented a hydrodynamic theory for a geometric idealized model of the cochlea. Their equations include the effects of dissipation in the cochlear partition and of viscous losses in the fluids filling the scala vestibuli and tympani. Solutions were at first given only for the case in which dissipation in the cochlear partition was disregarded. In a later paper however, Bogert (49) determined the effect of dissipation by means of a network representing the basilar membrane and also was able to give solutions to these equations. The equations of Peterson & Bogert (48) give the pressures in the fluids on either side of the cochlear partition and the displacement of the basilar membrane, both as a function of frequency and the distance along the membrane.

Zwislocki (50, 51) also has undertaken a mathematical analysis of the propagation of vibrations in the cochlea based on anatomical data and physical constants; he found that none of the existing theories of hearing can be regarded as adequate. The skeleton of his theory is as follows. The problem is shown to be of a predominantly hydrodynamic nature. He deduced a dynamic differential equation containing all the factors which influence the process of vibration. The factors contained in the equation are: the density and viscosity of the perilymph, the dimensions of the canal, and the impedance (mass, damping and elasticity) of the cochlear duct. The mass, however, could be neglected. The solution of the equation led to results which were in better agreement than before with the experimental findings. The eddies, demonstrated by Békésy, are to be regarded as a secondary phenomenon and they cannot stimulate the sensory cells. Zwislocki suggests that the forces of mass arising in the cochlear duct may be the mechanical factors which lead to stimulation of these cells. This means that he also denies the possibility of stimulation by displacement of the membranes caused by a pressure disturbance at the vibration maximum [however, see (52)]. Ranke (52) has recently in a short review discussed his well-known hydrodynamic theory in the light of Békésy's experimental findings and Zwislocki's new physicomathematical analysis. In many aspects, however, the conceptions of these authors are at variance.

The view that the decisive role for the capacity of hearing the various tones is played by vibrations of the tectorial membrane pressing on the hair cells of the organ of Corti has recently again been advanced by Mygind (53). Leiri (54) thinks that only the lower tones up to the fourstroked octave depend upon the oscillations of the tectorial membrane; however, the higher tones are transmitted to the inner ear according to the resonance theory (55, 56). De Vries (57), using polarized light and phase contrast, describes the structure of the tectorial membrane.

THE AUDITORY IMPULSES

The excitatory process in the cochlea.—Sound waves transmitted to the ear must be transformed in some manner into electrical energy before they can be recognized by the brain. However, we know very little about the

actual processes that transform the mechanical stimulus into a neural response. Three hypotheses (mechanical, chemical, and electrical) have been advanced to explain the nature of the excitatory process by which the cochlea initiates impulses in the auditory nerve fibers. According to the second hypothesis, the hair cells on deformation liberate in some unknown manner a chemical mediator which in turn stimulates the nerve endings in the cochlea (58). Gisselsson (59) was unable to demonstrate the formation of acetylcholine in response to acoustical stimulation. Nor does it sound reasonable in the light of our present knowledge of hearing to suppose the liberation or formation in the cochlea of such quantities of acetylcholine as can be demonstrated by methods of today. However, acetylcholine esterase could be demonstrated both in the perilymph and the endolymph (pigeon, cat, and guinea pig) in quantities large enough to suggest its participation in a transmission mechanism. In order to test the tenability of this assumption, experiments were done to find out whether esterase-inhibiting substances are capable of having any demonstrable effect on the cochlear response. The problem was attacked indirectly by studying the latency: the idea being that substances possessing an inhibitory effect on acetylcholine esterase might be expected to have an effect on the latency of the cochlear potentials. A method was devised for recording continuously the latency of cochlear potentials. Gisselsson supposed that the injection of such substances (e.g., physostigmine) prolonged the latency, and therefore, he came to the conclusion that acetylcholine participates in the transformation of sound, i.e., mechanical energy into electrical energy in the inner ear. In the light of other biochemical and neurophysiological findings, the reviewer does not object to the view that a chemical mediator may play a part in the transformation process, but there are, however, many pitfalls connected with the measurement of latency which have been neglected by the author.

According to the third hypothesis, the cochlear microphonic, generated by the hair cells in the organ of Corti, is an essential chain in the excitatory process. However, the cochlear microphonic is also considered to be merely an accidental circumstance. The reviewer is under the impression that the output of papers on cochlear microphonic has diminished in recent years. The reasons for this decline in interest are, of course, difficult to state, but one may venture the suggestion that audioelectric research concerning the cochlear microphonic in many sectors has entered into a cul-de-sac. The descriptive side of the subject is by now rather completely covered; an immense amount of analytical data has been collected. These facts do not signify, however, that our knowledge of the postulated role played by the cochlear microphonic in transformation of mechanical stimulus into neural response approaches saturation. On the contrary, everybody familiar with this field knows that much remains to be clarified. The wide discrepancy between the effect of frequency on cochlear microphonic and action potential throws some doubt on the hypothesis that aural microphonic is essential

for the stimulation of the peripheral terminations of the fibers of the auditory nerve (60). Other experimental facts supporting this opinion also have been presented by different laboratories.

All methods by means of which the audioelectric responses can be differentiated would seem to be of very great interest. Kahana, Rosenblith & Galambos (61) report reversible changes in the behaviour of the cochlear and neural potentials, recorded from the round window of the hamster. There were differences with respect to latency, duration, and amplitude between the two components as the temperature was varied over an appreciable range.

In an important study, Davis, Fernández & McAuliffe (62), using tone-pip stimulation (63), describe a new electrical potential (summing potential) in the cochlea which seems to represent the local excitatory process that initiates auditory nerve impulses. In a previous paper (64), it was found that when the cochlear microphonic (see below) approaches the post-mortem level, it undergoes partial or complete half-wave "rectification" for frequencies below 2,000 c.p.s. Only one-half of each wave still remains. The phase corresponding to condensation in the external canal is more depressed than the phase corresponding to rarefaction. Even at higher frequencies, there are also some kinds of "rectified" potentials, but they are quite independent of the cochlear microphonic and represent a third electrical potential which shows the property of summation at frequencies above 2,000 c.p.s. There is strong evidence that the summing potential differs from both the cochlear microphonic and action potential (62).

The audioelectric responses.—Three types of electric responses can be recorded from the inner ear during acoustical stimulation: the cochlear potential also known by the term microphonic, the action potential of the auditory neurons and, as mentioned above, the summing potential.

Békésy (65) describes the microphonics produced and measured by a vibrating electrode placed on different parts of the cochlear partition of a guinea pig. The microphonic voltage is produced as long as the constant static deformation on the basilar membrane continues. A single displacement of the basilar membrane produces a static voltage lasting for several seconds. These findings are of importance for the energetics of the microphonics. The nonlinear relation between the intensity of the stimulating tone and the voltage of the cochlear microphonic for sound pressure at high levels has been reinvestigated, and a more detailed picture is presented (66, 67, 68).

There is an opinion among some otologists (69) that the hearing improvement following fenestration is the result of drainage of perilymph which is under pressure in clinical otosclerosis. The experimental findings upon fresh human cadaver material by Békésy (45) reported in an earlier article (now translated into English) showed that increased hydrostatic pressure up to 4 atm. does not interfere with the mechanism by which sound is transmitted through the middle ear and through the cochlear fluid. Lempert,

Wever, Lawrence & Meltzer (70), working upon living monkeys, measured the cochlear potentials recorded from the round window before and after the perilymphatic pressure had been raised and found that the function of the hair cells of the organ of Corti is unaffected.

After a hard struggle to overcome all technical difficulties involved, the full length paper by Lempert, Meltzer, Wever, & Lawrence (71) on the human cochleogram and its clinical application has appeared. In a previous article, they have discussed the possibility of making use of the electrical activity of the cochlea in the diagnosis of diseases of the ear (72). In about one-third of the ears studied, they were successful in recording cochlear potentials in response to various kinds of acoustical stimuli from the round window in the course of surgical operations. The electrical activity of the human cochlea was of the same general character as of other ears previously studied, but the magnitude of the potentials was smaller, only of the order of a few microvolts. Under favourable conditions, the maximal voltage of the cochlear response in cats and guinea pigs may reach a value of 1 mv. The cochlear response of the monkey is smaller than the one observed in higher vertebrates and lower mammals. The authors suggest that this difference depends upon the peculiar bony enclosure of the cochlea of the primate ears. Recording from the promontory wall of the tympanic cavity of a more "intact" ear after passing the electrode through the tympanic membrane gave a very unsatisfactory response. They also tried Békésy's endoscope (18) in order to get a view of the round window niche for applying the electrode, but the method, due in part to the anatomical situation, was too hazardous. The cochleogram seems to have no general clinical application, but we must be grateful to the authors [see also Perlman & Case (73)] that our curiosity about the human cochlear response has been alleviated.

In a series of papers from the Central Institute for the Deaf, St. Louis, Davis and co-workers have studied all three types of electric responses but from different points of view. First, they worked out the limitations and pitfalls as well as the advantages of experimentation with multiple cochlear electrodes (74). When recording from opposite scalae of the same turn, they had hoped it would be possible to cancel aural microphonic completely (opposite in phase) and then obtain a pure action potential pattern because the action potential has the same polarity in each scala, but due to electrical leakage from one turn to the next through the bony partitions, it was not possible to get a complete mutual cancellation of the microphonic components of clicks. In a later paper by Békésy (75), the electrical constants inside the cochlea have been measured in order to find out how voltages at a given point are transmitted to other parts of the cochlea.

The mixture of the cochlear potential and action potential gives an irregularity in the wave form which leads to an uncertainty as to the relationship between the intensity of stimulus and magnitude of the microphonic. The interaction between them varies with frequency and with the position

of the electrodes. In a later paper, Davis and co-workers (60) succeeded in measuring separately the threshold of the two components for frequencies below 1,000 c.p.s. The cochlear microphonics were eliminated by a method depending on cancelling them by a signal derived from the electrical current that produces the sound stimulus. They found that action potentials could be depressed by quinine without much effect on the microphonic [see also (76)]. The action potential threshold in decibels for tones below 1,000 c.p.s. is a linear function of the logarithm of the frequency, whereas the threshold of the microphonic was almost independent of frequency from 1 to 5,000 c.p.s. This way of measuring the two threshold curves separately gives a more correct curve because otherwise the "threshold" is determined by the cochlear microphonic at high and low frequencies but by action potentials over the middle frequencies. There is a striking smoothing of the true threshold curve for the microphonics after administration of quinine because then the re-enforcement or partial cancellation of the two components has been eliminated.

Streptomycin on the other hand exerts a toxic effect which primarily reduces the aural microphonic response (77) and produces a small loss of hearing in the lowest and highest frequency-range (78, 79). A disturbance of hearing can also be produced by dimenhydrinate (Dramamine) (80) and ascaridol (81). The latter drug produced degeneration of the hair cells accompanied by a loss in the cochlear potentials. Bornschein & Krejci (82) have determined the latency of the action potentials by means of interference between action potentials and cochlear potentials. Their results are in agreement with earlier findings.

Effect of oxygen deprivation upon the cochlear potentials.—A number of papers have appeared dealing with this problem. No decline of the potentials was observed with gas mixtures containing more than 4 per cent of oxygen, equivalent to altitudes up to 40,000 ft. Severe oxygen deprivation causes a loss of the cochlear potentials, up to 40 db. (83). Recovery of the cochlear potentials could be influenced by using different perfusing fluids. The degree of the increase depended upon the oxygen content of the perfusion fluid (84). Both direct and indirect evidences have shown that the hair cells of the organ of Corti are responsible for the generation of cochlear potentials, and therefore, the changes due to anoxia take place in them.

This being so, we are presented with the peculiar problem of the nourishing of these cells because they do not possess any direct blood supply. Hence, it appears that oxygen diffuses from the stria vascularis over a mean path of about 0.33 mm. across the cochlear duct to reach the hair cells. The deterioration is independent of frequency and of intensity (83, 85, 86). By ligation of the aorta, Bornschein & Krejci (87) found no significant difference in the rate of the initial decline of the potentials when the animal before ligation was breathing air or was in a hypoxaemic state. This suggests a remarkable lack of oxygen reserves in the organ of Corti. They also showed by simultaneous recording of blood pressure that this reduction in amplitude

of the cochlear output is a primary result of anoxia and not of secondary changes in the circulation due to asphyxia (88). Gisselsson (59), however, is of the opposite opinion.

In addition to the use of quinine in order to eliminate the action potentials, it has been shown that repeated anoxia experiments are always followed by complete restitution of the cochlear potential, whereas the action potential gradually disappears, provided that the anoxia is not carried too far (89). This provides a simple method of eliminating the action potential without affecting the cochlear potential, a technique suitable for cochlear potential threshold measurements.

Microphonic activity of the labyrinth.—When confronted with the fact that the vestibular apparatus and the organ of hearing are so closely related, one finds it difficult to understand why two such totally different organs having functions in no way related to each other are suspended in the same medium (perilymph), occupy a common site, and share the same endolymph. In the one case, the interpretation of movement, direction, and position and, in the other, the interpretation of sound are the functions. Yet, they are intimately connected by the common endolymph, the perilymph and, above all, the cochlear duct, which is an outgrowth from the membranous sacs of the vestibular organ. Ever pursuing the utmost in economy, evolution has designed this contiguity. It is necessary to search for a common denominator of the complex functions as represented by the semicircular canals with their ampullae, the utricle, and the saccule which will correlate with properties peculiar to the organ of Corti.

In a series of interesting papers, the electrical response of the cristae in the ampullae of the semicircular canals to incident sound has been described. Bleeker (90) found, after opening the semicircular canal of a pigeon, that a microphonic response could be recorded, even following the destruction or extirpation of the cochlea, if sound is offered to this ear. The effect disappears when the crista in the ampulla concerned is destroyed, but can be shown again, although to a lesser degree, by subsequently opening another semicircular canal. Some qualitative details of the new "crista effect" were studied by De Vries & Bleeker (91), and they discussed its functional meaning with special reference to the Tullio reaction. Generally, the wave form deviated more from the pure sinusoidal shape than the cochlear response, but the phenomenon of fatigue seems to be the same as for the cochlear response. In other respects, too, there is a striking similarity between the two responses (92, 93, 94).

AUDITORY MASKING, ADAPTATION, REVERSIBLE FATIGUE, AND TRAUMA

Masking and reversible fatigue have the same fundamental properties, namely, the shift of the threshold of hearing (95), changes in loudness and pitch (96 to 99), and the effects upon localization in space (100, 101) due to either simultaneous or previous stimulation. They seem to be mediated by

one or several peripheral neural mechanisms, and there are several hypotheses offered to explain them. Although the problem is far from being explicitly stated, some recent papers have a bearing on the question (102, 103). Comparative experiments between adaptation and masking by Lüscher & Zwislocki (104, 105) demonstrate a far-reaching similarity between the two processes. These show a similar behaviour with respect to intensity and frequency, and a quantitative comparison led the authors to the conclusion that masking depends chiefly upon the adaptation of the ear to sound stimuli. Binaural determination of adaptation, by leading the stimulating impulse to one ear and the testing impulse to the other, showed that adaptation is a monaural and therefore a peripheral process. Earlier reports in the literature tend to discuss masking as depending upon the process of excitation of the cochlear nerve fibers, upon the refractory period, or as a product of a spatial interaction. Experiments by Hawkins & Kniazuk (106) indicate that the mechanism cannot be explained on the basis of the refractory state alone because this is too short to account for the slow recovery of the action potentials after masking. They expressed the belief that the mechanism that transmits excitation from the hair cells to the peripheral terminations of the fibers of the auditory nerve might be involved.

Rosenblith, Galambos & Hirsh (107) tried to correlate the temporary deafness after previous auditory stimulation with changes in the "electrical audiogram." If the cat's ear is exposed to pure tones of different frequency, intensity, and duration and the response to click-stimulation before and after exposure are compared, significant changes are evident. A relatively short exposure to a loud tone (100, 200, and 500 c.p.s.) depresses the neural part of the round window response to a weak click and also raises the threshold of the neural component. However, there is a rapid recovery after the end of exposure, and the neural component may continue to grow and go through a period of supernormality. The course of recovery (108, 109, 110) and the state of supernormality depend principally upon the frequency of the exposure tone. After exposure to tones of higher frequency but with the same intensity and duration, the neural response is depressed for a much longer period and no supernormality is in evidence. They also found a parallelism between the recovery of the first neural component recorded from the round window and the recovery of the neural response recorded at the auditory cortex. They compared the human threshold shift for clicks after exposure to loud tones with their results from the animal experiments and suggested the possibility of a relation between these two phenomena. By masking clicks with pure tones, Hirsh, Rosenblith & Ward (111) got fairly reproducible results for a given ear with normal hearing, but there was a great variability between different observers and even between the two ears of the same observer. However, when using bands of noise in order to mask the same click, there was a reasonable agreement and at a much lower cost. The last two papers (107, 111) and earlier representative work concerning auditory masking and fatigue have been reviewed by Rosenblith (112).

The frequency selectivity of the ear as determined by masking experiments was studied by Schafer *et al.* (113), and the efficiency of thermal noise in masking several pure tones of different spacing was determined by Schafer & Gales (114). Miller & Garner (115) showed that the effectiveness of the masking of tones by interrupted noise depends primarily on the duration of the silent interval and secondarily upon the frequency of the masked tone and the intensity of the noise. The masking audiograms of a pure tone of 400 c.p.s. and of a narrow band of noise with a center frequency of 410 c.p.s. were reinvestigated by Egan & Hake (116). The degree to which a band of noise masks a tone whose frequency is near the center of the band is related to two principal variables: the intensity of the noise and the width of the critical band. If one assumes that this critical band around the position of the pure tone comprises a constant number of nerve fibers, the intensity ratio is a direct measure of the density of frequencies on nerve fibers. If the masking noise is at least as wide as a critical band, then the value of the masked threshold should be given by the following expression: $MT = B + k$, where MT is the masked threshold, B is the intensity per cycle, and k is the width of the critical band. In the experiments of Egan & Hake, the value of k turned out to be 14 db. In a study by Hawkins & Stevens (117) using a wider band of noise, the value of k was found to be 17 db. The difference of 3 db. between the values of k found with a narrow and with a wide band of noise is too large to be assigned to the variability between observers or errors of measurement (118). Egan & Hake suggested that the smaller value of k was the result of beats, since the test tone is heard as a "buzz" or "rattle." When using a wider band of noise, their redetermined value of k came closer to the earlier findings by other investigators. For purposes of deriving excitation or loudness patterns, a better estimate of the maximum amount of masking is obtained, therefore, by using a wide band of noise whose pressure spectrum level is the same as that of the narrow band. Munson & Gardner (119), in a study somewhat similar to the work already referred to by Lüscher & Zwislöcki (104, 105), point out the difficulties encountered in the determination of the excitation or loudness pattern of a pure tone. They employed a novel technique in which a test tone of brief duration was presented a short time after the masking stimulus had been turned off. By this method, they obtained measures of residual masking which are evidently free of the complications due to different tones, aural harmonics, and beats. Licklider, Webster & Hedlun (120) have outlined a theory of binaural beats based on synchronous discharges in the two auditory nerves.

Acoustic trauma.—It is generally known that people working in noisy vocations commonly develop impaired hearing. This type of hearing loss has assumed increased importance and interest; several monographs and papers covering a large part of this field have appeared (121 to 125), but only a few of the results can be mentioned. Some of the observations and conclusions are strikingly similar. Zwislöcki (127) describes a new type of ear warden in the form of ear plugs which act as acoustic low pass filters (126).

By using the continuous or detailed audiogram, Dishoeck (128) recorded the total pattern of deafness due to different types of stimulation. The effect of blast trauma and synthetic noise upon human subjects and guinea pigs has been studied thoroughly by Rüedi & Furrer (129) and upon rabbits by Perlman (130). The severe loss of auditory function and the extensive histological change in the cochlea agree with the absence of visible damage of the middle ear (131). The short lasting shock pulse of a gunshot gave, without visible damage to the drum, a degeneration of the external hair cells and Deiter's cells at the end of the first coil up to the middle of the second coil (132). Half of these animals showed a loss of the pinna reflex (129); functional examination by means of the cochlear response (132) showed a marked dip at C^5 of 10 to 30 db. immediately after the trauma with a tendency towards becoming deeper and wider. The shape of the pulse, as well as the pressure, is of importance in producing middle-ear damage. A longer time period of the shock pulse, as from a detonation of explosives like pentryl or tetryl, gave more extensive damage to the cochlea. The tympanic drum and part of the middle-ear structure were damaged. Reissner's membrane, the basilar membrane and sometimes even the round window membrane were torn. The end-organ, however, appeared to have been initially spared, but later there was also damage of the hair cells and neural elements. Rüedi & Furrer thought this damage was due to pressure by the collapsed Reissner's membrane.

In addition to the effect of the peripheral damage to the sense organ, the temporary threshold shift resulting from exposure to acoustic trauma may also be attributable to central changes at higher levels. Hamberger & Hydén (133) investigated the cytochemical changes in the cochlear ganglion caused by acoustic stimulation and trauma. Stimulation with 6,000 c.p.s. at an intensity of 80 db. for 3 hr. gave rise to a cycle of changes. Eighteen hours after stimulation, the nucleoprotein content in a limited area of the cytoplasm was low. This decrease continued rapidly. After one week, no pentose nucleic acids were present in the cytoplasm, with the exception of agglomerations of nuclear membrane nucleotides in large concentrations surrounding the nucleus. Thus, it was the picture of a nerve cell during an intensive production of cytoplasmic nucleic acids. During the second week, no measurable amounts of nucleotides were present in the cytoplasm. The nucleolus did not, however, appear to undergo any changes. During the third week, the original content of nucleoproteins in the ganglion cells was restored. This restitution started with the formation of nuclear membrane nucleotides. The extensive effect upon the cells by the stimulus used is very remarkable. In a following work, Hamberger, Hydén & Nilsson correlated the cytochemical changes with hearing acuity and cochlear function by means of pinna reflex and cochlear microphonic (134).

Ultrasonics.—The biological and physiological effects of intense high frequency air borne sound (135, 136, 137) have been discussed by Davis (138) and Dickson & Chadwick (139). Previously, it had been suggested

that the disturbances of hearing and equilibrium induced, for example, by jet-engine noise were due to the presence of ultrasonic waves. We have, however, no grounds at the moment for supposing that ultrasonic frequencies may constitute a practical hazard to hearing, and as pointed out by Davis, Parrack & Eldredge (125), the effect is largely due to high intensities and not to high frequencies as such.

AUDITORY TRACTS

Galambos & Davis (140) have found by histological methods that the auditory nerve in the stretch from the internal meatus to the medulla contains ganglion cells, and therefore, we have very good reason to believe that what they formerly called activity of single auditory nerve fibers was recorded not from single fibers (first-order neuron) but from the cell bodies of the second-order neurons belonging to the cochlear nucleus. Except for the suggestion of a peripheral inhibitory mechanism, their earlier description of the functional relations in the auditory pathway remains unchanged, however. Their brief note is of great interest because there has been the same trouble when trying to record the activity in single fibers from other sense organs (141, 142, 143). It does not seem possible that the needle or micro-electrode technique allows a recording of the electrical activity of separate nerve fibers *in situ* well enough to account for the spikes of 0.1 to 0.3 mv. that actually were obtained. At present, the most commonly used electrolyte filled capillary electrodes or metallic electrodes have a diameter of 5 to 50 μ . The electrode thus records the electrical activity from a cell body or some cell body component, depending on the localization of the point. If cell bodies are lacking in the region around the electrode point, some electrical activity will, of course, be obtained but hardly as large and well isolated responses as those actually seen.

Some new findings concerning the anatomical organization of the auditory pathway have been presented, but they are known on a physiological rather than on an anatomical basis. A review of the function of the acoustic nervous connections as shown by electrical recording has been given by Galambos (144). Galambos, Rosenblith & Rosenzweig (145) have presented evidence that one of the places for functional interaction between the ears already is to be found in the cochlea itself. Electrophysiological results make it probable that each cochlea is connected by a neural pathway to its mate, but anatomical findings are still lacking concerning this cochleo-cochlear pathway. Ades & Brookhart (146) recorded the electrical response to click stimulation from various points along the central acoustic pathway and analyzed the ipsilateral and contralateral contributions to the activity so evoked. They discussed the function of the inferior colliculus as a midbrain center for acoustic reflexes. Galambos & Rosenblith (147), also using click stimulation, studied the slow wave and spike discharge from the cochlear nucleus and inferior colliculus.

Experiments by Lipman (148) using motor condition methods in order

to study the acoustic function of the temporal cortex of dogs led him to the conclusion, in accordance to earlier findings, that two parallel and functionally equivalent tracts, one cortical and one subcortical, may serve to mediate auditory conditioned responses. It is therefore suggested that frequency-distribution in the cortex can be adequately determined only when the subcortical mechanisms are either functionally or surgically eliminated. Walzl (149) has summarized some of the more important work upon the representation of the cochlea in the cerebral cortex.

Tunturi (150), using the method previously reported (151, 152) for distinguishing afferent connections from or in the presence of electric fields, has re-examined the localization of frequencies in the middle ectosylvian area, and Bremer *et al.* (153, 154, 155) have presented an oscillographic analysis of the responses. The inferior part of the posterior ectosylvian gyrus is dependent on the primary auditory area for its specific activation and constitutes a secondary area in the sense of an association area (156). Gellhorn (157) showed that no significant difference existed in the sensitivity of the acoustic and optic projection areas to anoxia.

Hampson (158) stimulated the auditory regions of the cerebral cortex and picked up potentials from the posterior cerebellar vermis. The pathway between the cochlear nucleus and cerebellum has not yet been traced. The fact that a response from the lobus simplex and the tuber vermis can be eliminated by lesions in the inferior colliculus would indicate that it passes through this region (159). How it gets there we do not know. The organization of the auditory tracts has also been studied from an anatomical point of view (160, 161, 162).

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THE PITUITARY-ADRENAL SYSTEM¹

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This review is concerned primarily with those reports of the year which relate, either directly or indirectly, to the physiological activities of the pituitary-adrenal system. While activation or depression of the pituitary release of adrenocorticotrophic hormone (ACTH) may be measured in experimental animals by determining changes in the concentration of adrenal ascorbic acid and cholesterol, or by histologic and histochemical analyses of the adrenals, one is forced to base his interpretations of experiments in man upon the observed peripheral metabolic activities of the released adrenocortical hormone and upon its urinary end products, pending more precise methods of measuring adrenocortical hormone in the peripheral blood. Thus, with particular respect to investigations in man, it becomes necessary to include in this review, not only the results observed from endogenously-produced and parenterally-administered ACTH, but also those studies which report on the results of administration of pure steroidal compounds possessing metabolic effects akin to those observed during administration of ACTH.

ACTIVATION OF THE PITUITARY-ADRENAL SYSTEM BY STRESSING CIRCUMSTANCES

Long and his group (1, 2) have made significant contributions to our knowledge of the mechanisms that control secretion of ACTH in the rat. In carefully controlled experiments these workers found that: (a) Administration of epinephrine augments cortical secretion only in the presence of the anterior hypophysis. (b) Endogenous epinephrine, released by various forms of stress, fails to augment cortical secretion in the hypophysectomized animal. (c) Insulin hypoglycemia activates the pituitary-adrenal system via release of epinephrine. Prior administration of glucose to abolish insulin hypoglycemia prevents pituitary-adrenal activation. (d) Administration of glucose, however, fails to prevent the discharge of ACTH produced by exposure to cold. (e) Pretreatment with adrenal cortical extract blocks release of ACTH ordinarily produced by either insulin hypoglycemia or epinephrine; this, despite the fact that the metabolic activities of epinephrine are in evidence. Thus, they believe that adrenal cortical extract acts directly upon the pituitary gland to inhibit release of ACTH despite the presence of an activating concentration of epinephrine in the blood.

They emphasize the fact that pituitary release of ACTH can and does

¹ The survey of the literature pertaining to this review was concluded in June, 1951.

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occur in the absence of epinephrine, but point out that conflicting opinions regarding the role of epinephrine as a physiological activator of ACTH release can be resolved if one takes into account the time factor and the intensity of the applied stressful stimulus in the various experiments. They were able to demonstrate that measures that prevent release of epinephrine (adrenal demedullation, spinal cord section, and diencephalic lesions) abolish all evidence of rapid activation of the pituitary-adrenal system upon the application of a stimulus that is quickly effective in intact animals. On the other hand, continuation of the stressful stimulus leads eventually to pituitary-ACTH release.

Finally, in an ingenious set of experiments, they used hypophysectomized animals containing anterior pituitary tissue transplanted into the anterior chamber of the eye. These animals activated their adrenal cortices in response to painful stimuli or subcutaneous administration of epinephrine. Furthermore, a minute amount of epinephrine placed into the eye containing the graft produced cortical stimulation. The same quantity of epinephrine placed into the ungrafted eye was without effect. Following removal of the eye containing the graft, subcutaneous epinephrine failed to activate the adrenal glands.

The authors propose a dual mechanism which, under conditions of stress, operates to control release of ACTH; first, an autonomic mechanism that is rapid and depends upon a reflex secretion of epinephrine, the latter activating the anterior pituitary directly; and, second, a metabolic mechanism based upon the rate of utilization of adrenal cortical hormones and their resultant level in the blood. These experiments have been reviewed in detail to serve as points of reference in the interpretation of many other reports dealing with the problem of stress.

Dury (3) found that, while either epinephrine or insulin hypoglycemia produced eosinopenia in the intact rat, only epinephrine was effective in the adrenal-demedullated rat. He concluded that insulin hypoglycemia stimulates epinephrine secretion. Gray & Munson (4) calculated that the "reaction-time" of the pituitary in releasing ACTH following intravenous histamine was of the order of 10 sec. or less. Carey *et al.* (5) noted a decrease in adrenal ascorbic acid and cholesterol in rats and guinea pigs given large doses of glutathione, and Dordoni & Fortier (6) observed a decrease in adrenal ascorbic acid with either physostigmine or atropine. Since simultaneous administration of atropine enhanced the physostigmine-induced depression of adrenal ascorbic acid, the authors believe that their results preclude the possibility of cholinergic control of ACTH release. Constantinides *et al.* (7, 8) observed that oral administration of glucose to hypophysectomized rats enhanced greatly the response of the adrenals to ACTH. In similarly operated animals, they were unable to alter the adrenal response to ACTH by simultaneously changing the blood sugar level with either epinephrine or insulin. They believe that the change induced by oral glucose is related to an increase in total body carbohydrate or intermediary metabolites thereof.

Several interesting points concerning various forms of stress in animals have come to light. Love (9) was unable to prevent the progressive eosinopenia which follows (over 4 hr.) the administration of epinephrine, even though bilateral adrenalectomy was completed within 10 min. after the epinephrine was given. He concluded that an appreciable quantity of adrenal steroid is secreted within 10 min. of epinephrine administration. Gordon's (10) conclusion that the adrenal medulla is not essential for activation of the pituitary gland by insulin, histamine, or exposure to cold is in agreement with those of others (2) and probably represents ACTH release via the "metabolic phase" (2). He (11) did find, however, that denervation of a rat's extremity, prior to the application of mild trauma to it, diminished the adrenal response to the traumatic procedure, while denervation had no effect when the leg was traumatized severely. These results, too, are explainable on the basis of the concept presented by the New Haven group (1, 2). Fortier *et al.* (12) were unable to decrease stress-induced depletion of adrenal ascorbic acid by antecedent (1 hr.) administration of cortisone (as much as 25 mg. per 100 gm. of rat). Inasmuch as the larger dose produced narcosis 30 to 45 min. following its administration, it was implied that high blood levels of steroid existed. The results were interpreted as indicating that hypocorticism is not the sole agent responsible for activating release of ACTH. Since in these experiments in which the applied stress was severe, one does not know the actual blood levels of adrenal hormone (despite the presence of narcosis) the conclusions would appear premature. The degree of stress relative to the degree of cortisone-induced depression of ACTH release is probably of great importance in experiments of this type.

Danford & Danford (13) noted a twofold increase of 17-ketosteroid excretion of rabbits during a 48-hr. period of forced water diuresis. This was not altered when large amounts of potassium chloride were added to the administered water. Danford & Danford (14) also kept male rats on a sodium deficient diet for 34 days and observed a twofold increase of urinary 17-ketosteroids by the end of 14 days. Thereafter, however, excretion of 17-ketosteroid declined below control values. At 34 days, the animals were sacrificed and exhibited adrenal hypertrophy with depletion of ascorbic acid, and thymic involution. Thus, prolonged sodium restriction was thought to result in increased adrenal cortical activity associated with an initial increase but a subsequent decrease of 17-ketosteroid excretion. Ingle & Nezamis (15) noted a decrease of glycosuria in mildly diabetic force-fed rats when formaldehyde was used as a stressing agent. In similarly treated adrenalectomized diabetic rats maintained with adrenal cortical extract to keep glycosuria at the preadrenalectomy level, the decrease in glycosuria was greater but rose toward the prestress level before injections of formaldehyde were stopped. They believe that increased elaboration of adrenal hormone during stress goes to meet the increased need for the hormone and tends to maintain homeokinesis rather than to produce a state of hypercorticism, and that some degree of adaptation to stress can occur in the absence of the adrenal cortices (but in the presence of cortical hormone). Engel (16), meas-

uring the rate of urea formation in bilaterally nephrectomized rats, compared the effects of applied stress with those of administered ACTH. The speed and magnitude of protein catabolism produced by nonspecific stress cannot be duplicated by large doses of ACTH given intravenously. This stress effect upon nitrogen metabolism is not solely via increased elaboration of cortical hormone, but the presence of an 11-oxysteroid is necessary to make possible the initiation and maintenance of the response to stress through a mechanism which is as yet unknown. In the presence of excessive amounts of adrenal hormone, stressful situations, which, *per se*, do not produce measurable changes in nitrogen metabolism, now become associated with such changes.

Sellers and associates (17, 18, 19) have studied the role of the adrenal cortex and the thyroid under several conditions of stress. They observed that experimental burns produced no greater increase in urinary nitrogen in thyroid-fed rats than in the control group. Thyroidectomized rats showed a smaller increase in urinary nitrogen in response to the burn. Adrenalectomy abolished the nitrogen loss which follows the experimental burn. On the other hand, neither thyroidectomy nor adrenalectomy affected the sharp increase of urinary nitrogen that occurs when rats are exposed to a cold environment. It is suspected that different mechanisms are involved in the increased protein catabolism produced by the two types of stress. Rats acclimatized to cold (1.5°C.) survive for 12 days in the cold environment following adrenalectomy, while unacclimatized adrenalectomized rats exposed to the cold are dead in 2.4 days. While the authors postulate that much less cortical hormone may be required for survival after acclimatization, it would appear more likely that much more cortical hormone is required to establish the state of acclimatization which then allows for more prolonged survival in the cold. Pickford & Vogt (20) have suggested, on the basis of very indirect evidence, that epinephrine, besides releasing ACTH, may act upon the adrenal cortex by some other means.

De Groot and his associates (21) found that electric stimulation of the posterior region of the tuber cinereum or of the mammillary body of rabbits elicited a lymphopenia which was similar in time relations and magnitude to that following an emotional stress stimulus (22). Transverse lesions in these areas diminished or abolished the emotional-lymphopenic response. Similar lesions in the pars distalis and pars intermedia, as well as lesions that interrupt the infundibular stem, were compatible with normal responses. They believe that these experiments constitute evidence in favor of the idea that ACTH release is under neural control via the hypothalamus and the hypophyseal portal vessels of the pituitary stalk. Castor *et al.* (23) reasoned that if a humoral substance controlling ACTH release is secreted in the hypothalamus, administration of ACTH or cortisone to normal rats should produce microscopic evidence of reduced secretory activity in the hypothalamus. ACTH produced chromatolysis in the cells of the paraventricular nucleus. Cortisone affected this nucleus, too, but induced more widespread chromatolysis and vacuolation of thalamic and hypothalamic nerve cells.

These changes could be interpreted as meaning a decreased rate of synthesis of a protein secretion or as indicating diminished capacity for discharge of nerve impulses.

A few studies have appeared dealing with reactions of man to stressing circumstances. In confirmation of earlier observations Coppinger & Goldner (24) report a consistent fall of circulating eosinophils following surgical trauma in otherwise normal people. They believe that the degree of eosinopenia is related directly to the length and severity of the trauma. Hardy (25) studied the degree of postoperative eosinopenia in relation to both the intensity of postoperative retention of sodium, chloride, and water, and to the amount of potassium diuresis. He found a good correlation. In addition, he (26) calls attention to the sharp diminution of the volume of fluid secreted into the intestinal tract during the first postoperative day. Johnson *et al.* (27) using the electrolyte concentrations of serially obtained samples of sweat as an index of changes in the activity of salt-active steroids, studied patients before and after major surgery. Since in the postoperative period the change in the pattern of sweat electrolytes was the same as that resulting from injections of either ACTH or desoxycorticosterone, it was concluded that the commonly observed postoperative retention of salt and diuresis of potassium is due to increased activity of salt-active cortical hormone.

Whitelaw (28), on insufficient evidence, concludes that in severe burns deficient quantities of ACTH are produced endogenously to meet the need of this acute stimulus. Uotila & Pekkarinen (29) studied the pathologic changes produced in humans by intense, continuous stress ending in death. The weight of the adrenals increases rapidly reaching a maximum after 48 hr., and hypertrophy of cortical cells is manifest. The concentrations of epinephrine, ascorbic acid, and cholesterol in the adrenals falls to about 50 per cent of "control" values. There was evidence of increased activity of the thyroid, both histologically and on the basis of total weight. Since eosinopenia, following administration of typhoid H antigen in patients with inflammatory disease of the eye, correlates well with the improvement produced by such "alarming stimuli," Arendshorst & Falls (30) conclude that the effects of such therapy depends upon the release of 11,17-oxysteroids. On the other hand, Altschule *et al.* (31) and Soylemezoglu & Wells (32) report that mechanisms other than, or in addition to, pituitary-adrenal stimulation are involved in producing the changes in circulating leukocytes which follow administration of such agents.

In a study of the eosinopenic effect of physical and emotional stress in well-trained college oarsmen, Renold *et al.* (33) concluded that emotional stress alone or in combination with muscular activity, but not muscular activity alone, may lead to effective adrenal stimulation. They call attention to the importance of the cerebral cortex in the stress reaction. Borth & Mach (34) looked for changes in urinary 17-ketosteroids, urinary corticoids, and peripheral blood of normal men moved from an altitude of 400 m. to medium altitudes (1,850 m.) and during a mountain climb to 2,750 m. A slight decrease of 17-ketosteroid was observed at 1,850 m. and a sharp de-

crease at 2,750 m. The corticoids and peripheral blood did not change appreciably. The results were attributed to an adaptive shift in the utilization and metabolism of cortical hormones. In short-term experiments, using a decompression chamber, Biget (35) observed an increase in the hourly excretion of 17-ketosteroids in men subjected to simulated altitude of 8,000 m.

PRODUCTION AND RELEASE OF CORTICAL HORMONE BY THE ADRENAL GLAND

Perhaps the most fascinating experiments in this field have been concerned with direct observations of functional activities of living cortical tissue. Pincus, Hechter, Zaffaroni, Jacobsen, and their associates (36 to 39) studied steroidogenesis in surviving beef adrenal glands maintained by perfusion. They observed the following:

(a) Perfusion of either 11-desoxycorticosterone or 11-desoxy-17-hydroxycorticosterone (Compound S) through the gland resulted in hydroxylation at C-11 with the production of corticosterone (Compound B) and 17-hydroxycorticosterone (Compound F), respectively. No further conversion of 11-hydroxylated products occurred. These results have been observed by McGinty *et al.* (40) and by Savard *et al.* (41) who incubated the precursors with adrenal tissue homogenates.

(b) Perfusion with pregnenolone and progesterone leads to production of a number of more highly hydroxylated compounds, principally Compounds B and F. Addition of ACTH to the perfusion medium does not enhance hydroxylation of the precursors.

(c) Perfusion with ACTH produces an increase in the perfusate of a number of steroidal compounds but the increased output of Compounds B and F are far in excess of the others. Prolonged perfusion with ACTH stimulates release of Compound F as the major end product. Similar increases of Compounds B and F in the adrenal venous blood of dogs during administration of ACTH have been observed by Reich, Samuels, Nelson, and Zaffaroni (42, 43). Again Compound F appeared to be the major product.

(d) Either C¹⁴ labelled acetate or C¹⁴ labelled cholesterol can be transformed to Compounds F and B by the isolated adrenal. Thus, it seems likely that cholesterol is an intermediate in the reactions leading to steroid synthesis from acetate. In this connection Vestling & Lata (44) observed that homogenates of guinea pig adrenals produce Compound F as cholesterol disappeared from the media, and Haines *et al.* (45) found that slices of hog adrenal cortex used C¹⁴ labelled acetate to produce C¹⁴ labelled Compound F.

Using a technique in which one isolated adrenal gland of a dog is perfused with blood from the same animal, Vogt (46) noted that ACTH added to the perfusing blood increased the release of adrenal hormone while no effect was observed upon the addition of glucose, lactate, amino acids, sodium ascorbate, epinephrine, nicotine, colchicine, or morphine. Histamine appeared to activate hormone release sometimes. Of possible physiologic significance was the fact that reduction of the sodium-potassium ratio of plasma from the normal of 45 to 10 (by increasing the potassium concentra-

tion) produced a great increase in secretory activity of the gland. This activation was not observed when plasma sodium concentration was reduced to levels commonly found in the adrenalectomized animal. Of further interest was the observation that compounds bearing labile high-energy phosphate bonds (adenosinetriphosphate and creatine phosphate) produced significant increases in secretory activity of the isolated perfused adrenal while adenosine, adenosinediphosphate, or inorganic phosphate gave negative results. Vogt believes that the high-energy compounds may be essential for corticoid synthesis. These findings may be correlated with those of Tepperman & DeWitt (47) who observed increased oxygen consumption and decreased content of ascorbic acid of dog adrenal slices when ACTH was added to the medium, and with those of Reiss & Halkerston (48) who found that, while P^{32} uptake by the adrenals of hypophysectomized rats is considerably below that of normal rat adrenals, it can be greatly and quickly augmented upon administration of ACTH.

Several contributions have appeared that relate to the question of the dependence of electrolyte regulation upon the zona glomerulosa and upon the functional relationship of the latter to the pituitary gland. Feldman (49) concluded on the basis of a histological study that the entire adrenal cortex of the rat is under the control of ACTH. Earle *et al.* (50) in a study of hypophysectomized dogs observed atrophic changes in all three cortical layers of the adrenals. Functionally, however, the animals exhibited normal ability to withstand restriction of sodium and to excrete potassium, but were unable to excrete normally an orally administered water load. On the other hand, Brownell *et al.* (51) noted, after adrenal enucleation which leaves a sufficient amount of zona glomerulosa to maintain growth, that serum sodium concentration falls and remains below normal for several weeks. They concluded that more centrally located cortical tissue is necessary for maintenance of serum sodium. O'Donnell & Fajans (52) report that in man the cells of all three zones of the cortex are found to be hypertrophic following prolonged administration of ACTH.

INHIBITION OF THE PITUITARY-ADRENAL SYSTEM

In line with the hypothesis propounded earlier by Sayers that low or high blood levels of cortical steroids are largely responsible for activating or depressing pituitary release of ACTH, Cheng & Sayers (53) find that implantation of pellets of desoxycorticosterone acetate (DCA) increases the concentration of ACTH in the pituitary of the intact rat. This procedure also inhibits the marked depletion of pituitary ACTH which normally occurs 24 hr. after adrenalectomy. Hall *et al.* (54), however, found that large doses of DCA fail to inhibit the stress-induced decrease in adrenal ascorbic acid of the rat. But it should be recalled, first, that DCA, in relation to other active steroidal compounds, is the weakest inhibitor of ACTH release and, second, that, as pointed out by McDermott *et al.* (2), acute stress is associated with an autonomic release of ACTH which may be independent of the circulating level of cortical steroids.

Zizine *et al.* (55) found that testosterone propionate was capable of main-

taining partially the adrenal weight of hypophysectomized, gonadectomized rats and concluded that there is a direct action of male sex hormone upon the adrenal cortex. In man, Howard *et al.* (56) observed no effects of testosterone and pregnenolone which could be attributed to a change in function of the pituitary-adrenal mechanism, but Faloona *et al.* (57) found that administration of testosterone resulted (in 6 of 10 experiments) in a subnormal eosinopenic response to epinephrine. They concluded that testosterone inhibits release of pituitary ACTH.

Evidence of depression of the pituitary-adrenal axis when large doses of cortisone are used continues to be convincing. In rats, Winter (58) and Lewis (59) and their respective associates observed significant adrenal atrophy in response to administration of cortisone and the latter group (59) demonstrated, in addition, that hypophysectomized rats maintained with ACTH failed to develop adrenal atrophy when cortisone was administered. Antopol *et al.* (60) gave massive doses of cortisone to mice. Within 24 to 48 hr. there occurred congestion of both the adenohypophysis and the adrenal cortex. The pituitary then became smaller and there occurred shrinkage of the eosinophilic cells. After 48 hr. the adrenal cortex began to shrink but the glomerulosa and outer fascicular layers did not share in the atrophic process. This is similar to the findings in the rat reported by Winter *et al.* (58).

In view of the effect of cortisone upon the adenohypophysis to which reference has been made (60), it is of interest to review other reports concerned with cytologic studies of the anterior pituitary. It is reported that unilateral adrenalectomy, either in the fetal (61) or in the full-term rat (62), results in compensatory hypertrophy of the intact adrenal. During the first 50 days following unilateral adrenalectomy, Brokaw *et al.* (62) observed an increase in the percentage of eosinophilic cells of the adenohypophysis. The normal ratio of eosinophilic to basophilic cells returned at about the time that full hypertrophy of the intact adrenal had been accomplished. Thus, it was believed that increased activity of the eosinophilic cells had been responsible for the unilateral adrenal hypertrophy. The same group of workers (63) report hypertrophy of the adrenals of the intact rat which is in parabiosis with an adrenalectomized rat. On the other hand, Halmi (64), working with rats, and Laqueur (65, 66), with man, suggest that the basophilic cells are responsible for the elaboration of ACTH. The latter worker observed the typical hyaline changes of the basophilic cells (described originally by Crooke) as early as five and one-half days after the beginning of therapy with cortisone. He attributes these changes to phenomena associated with the storage of ACTH.

The vast clinical experience with cortisone has led to a number of observations which suggest that the steroid is capable of depressing the activity of the pituitary-adrenal mechanism. Sprague *et al.* (67, 68) point out that, in addition to gross and microscopic evidence of atrophy of the adrenal cortex following chronic administration of cortisone, one can demonstrate decreased functional activity of the cortex in a number of ways. They showed, too, that cortisone does not diminish adrenal cortical function

in panhypopituitarism maintained with ACTH. Thorn *et al.* (69) have made the interesting observation that in some patients with Addison's disease a relatively normal, though temporary, adrenal response to test doses of either ACTH or epinephrine may follow adequate substitution therapy with cortisone. This suggests that in relatively mild cases cortisone affords physiologic rest to an exhausted adrenal remnant (via inhibition of ACTH release) and the accumulation of sufficient adrenal hormone to allow for a short period of responsiveness to ACTH.

Wilkins *et al.* (70, 71) have taken advantage of the capacity of cortisone to depress adrenocortical activity by applying this phenomenon in the treatment of congenital adrenal hyperplasia with the adrenogenital syndrome. They have been able to reduce significantly the increased excretion of 17-ketosteroids characteristic of the syndrome with daily doses of cortisone varying from 25 to 100 mg. per day. The small doses of cortisone required in some cases to accomplish this result is surprising and gives rise to a number of speculations, the most important of which is the probability that the adrenals in this condition are not only producing an abnormal steroid but that they are producing too little of those steroids capable of inhibiting production and release of ACTH. Thus, Bartter *et al.* (72) on the basis of detailed metabolic studies suggest that the syndrome involves a primary defect of adrenocortical function with a secondary increase in the production of ACTH. It is of interest in this connection that some of these cases exhibit periodic Addisonian crises owing to excessive renal loss of sodium and chloride. In such a case, administration of ACTH intensifies the urinary loss of sodium and chloride as demonstrated by Lewis *et al.* (73). This again suggests production of an abnormal adrenal steroid. Another observation worthy of mention for its physiological implications is that spontaneous stress (intercurrent infection) produces prompt, temporary elevation of urinary 17-ketosteroids in a patient with congenital adrenal hyperplasia despite the fact that the daily level of urinary 17-ketosteroids is being satisfactorily depressed by continuous cortisone therapy (70, 71). It is too early to evaluate the long-term effectiveness or practicability of this form of treatment in congenital adrenal hyperplasia, but it is obvious at present that important information regarding pituitary-adrenal physiology is being obtained from study of these individuals.

PERIPHERAL EFFECTS OF ACTH AND ADRENAL STEROID COMPOUNDS

In their reviews, Sprague (74) and Ingle (75) have brought up to date the accumulated information on the physiological properties of ACTH and cortisone.³ In this section of the present review only those reports of the year which present new facts or ideas will be cited.

General.—Talbot *et al.* (76) suggest the probability that there exist more than one ACTH in the human body. This idea is based on the knowledge that, although present preparations of ACTH when given to infants, chil-

³ A number of other reviews and symposia on pituitary-adrenal physiology have appeared during the past year (180, 211 to 218).

dren, or adults stimulate a simultaneous increase in urinary excretion of 17-ketosteroids and 11-17 oxysteroids, parallel increases of these two urinary components do not occur spontaneously during stress nor during development from birth to adult life. Young (77) believes there are two types of ACTH extractable from pituitary tissue, each having different physiologic effects upon the adrenal cortex. Bartter *et al.* (78) in a study of the metabolic effects of ACTH in panhypopituitarism suggest that all of the effects except increase of 17-ketosteroids could be explained on the basis of cortical release of an 11,17 oxysteroid. Since Conn *et al.* (79) have demonstrated a large increase in urinary 17-ketosteroids during administration of Compound F, the possibility that this compound can duplicate all of the effects of ACTH exists. Ransohoff *et al.* (80) noted differences in the 17-ketosteroid and glycosuric responses to ACTH in man when the intake of sodium was varied from low to high and vice versa. They suggest that the sodium ion may be actively involved in the response to ACTH and in the activity of the adrenal cortex, or in both. Luft *et al.* (81), studying the metabolic effects of electrophoretically pure ACTH protein in a rheumatoid arthritic, noted the characteristic effects upon electrolyte and water metabolism but no effects upon organic metabolism at doses of 3 and 6 mg. per day. At a dosage level of 12.5 mg. per day, there occurred increased urinary excretion of nitrogen, phosphorus, calcium, creatine, glucose, uric acid, and other reducing substances, as well as a more intense effect upon electrolyte and water metabolism. At higher doses (25 to 50 mg. per day), there was no greater effect except upon reducing substances. Albright, Bartter, and associates (78, 82) having compared the metabolic effects of Armour ACTH with those of pitressin, prolactin, and electrophoretically pure ACTH conclude that the experiments are consistent with the possibility that urinary calcium losses result, not from ACTH activity, but from the pitressin present as a contaminant in the Armour product. Everse & Overbeek (83) observed that a single intraperitoneal dose of 0.001 mg. of ACTH given 24 hr. after removal of the rat's hypophysis caused a significant increase in performance of a muscle work test, while 48 hr. after hypophysectomy the same dose was essentially ineffective in increasing muscle work.

Considerable interest has been generated by the observation of Gordon, Kelsey & Meyer (84) that slow, continuous administration of ACTH intravenously may be as much as 20 times more effective in terms of over-all adrenocortical stimulation than ACTH given intramuscularly at 6-hr. intervals. This has been confirmed by Querido (85) and Renold (86) and their associates. The latter group (86) has worked extensively on this problem and has found that the longer the duration of intravenous infusion of a 20-mg. dose of ACTH (up to 48 hr.), the longer did eosinopenia persist upon cessation of infusion and the greater was the rise of 17-ketosteroids. Twenty mg. of ACTH given intravenously in 1 min. gave no evidence of cortical activation. When the duration of infusion was fixed at 8 hr., it was found that doses larger than 20 mg. did not increase further adrenocortical activation. Using the 8-hr. infusion technique as the baseline, it was ob-

served that the degree of cortical stimulation produced by 20 mg. of ACTH was comparable to that obtained when 100 to 200 mg. per day were given intramuscularly in divided doses at 6-hr. intervals. Patients who had developed lack of responsiveness to intramuscularly administered ACTH responded normally when the material was given intravenously.

Work on biologically active split products of ACTH protein continues to progress. Lesh *et al.* (87) report that the size of the active moiety of ACTH protein (number average molecular weight, 2500 to 10000) is considerably greater than that of ACTH peptides (molecular weight, 1000) described earlier. They suggest that the latter may be contaminated with a small amount of a large molecule having very high biological potency. Smith *et al.* (88) using the method of ultracentrifugation, electrophoresis, and diffusion for the isolation of hog ACTH conclude that it is likely that ACTH is stored in the gland as a protein having a molecular weight of about 20000. At pH 0.1 to 0.2 the material splits rapidly to yield particles of low molecular weight and there is no loss of biological potency. Geschwind and associates (89) using 5 per cent trichloroacetic acid as the solvent prepared a number of nonprotein fractions possessing ACTH activity from sheep pituitary glands. Li *et al.* (90) used paper partition chromatography to achieve better purification of a pepsin digest of sheep ACTH. Molecular weights by ultracentrifugation of the various fractions indicated that the purest fraction had an average molecular weight of about 2000. Forsham, Renold & Lesh (91) studied the metabolic effects of a polypeptide fraction of ACTH which by the ascorbic acid depletion method and by the human eosinopenic index assayed about 100 times the potency of the LA-1-A standard. The over-all metabolic effect in man was shown to be about 25 times as potent as the LA-1-A standard. All of the metabolic effects of commercial ACTH were observed to be produced by the fraction. Great cortical activation was produced by continuous intravenous administration for 8 hr. at a rate of 1 μ g. per minute. Payne, Raben & Astwood (92) have described a method for the extraction of ACTH from acetone-dried pig anterior pituitary powder which yields an extract having biological activity of about 80 times the LA-1-A standard.

The peripheral effects of administration of pure steroidal compounds have been studied intensively. Reference has already been made to many of the biological properties of cortisone. The excellent review of this subject by Ingle (75) is recommended. A major advance in the therapeutic use of cortisone was the discovery by Freyberg *et al.* (93) that the compound when given orally in essentially the same dose as by the intramuscular route produced similar metabolic and antiarthritic effects. Kochakian & Robertson (94) found that cortisone pellets implanted into adult castrate mice produced an intense loss of carcass protein during the first 7 days after which no further protein loss occurred. The total protein loss paralleled both the involution of lymphatic tissue and the extra nitrogen excreted. Dehydrocorticosterone (Compound A) was one-twentieth as effective on tissue composition as cortisone, and Compound S was without effect. Higgins, Woods &

Kendall (95) studying the biologic activity of Diene ($\Delta 4$ -6-dehydrocortisone) observed very mild effects. Conn *et al.* (96) observed that corticosterone given intramuscularly to normal men exerts, as compared with cortisone, a greater influence upon electrolyte and water metabolism and a lesser (but definite) influence on organic metabolism. In doses as high as 200 mg. per day it does not produce eosinopenia. When given to patients with Addison's disease at a dosage level of 25 mg. per day for 60 days, it exhibited the desirable effects of a combination of cortisone and DCA and proved to be excellent substitution therapy.

Fourman *et al.* (97) studied the metabolic effects of two 50-mg. doses of free Compound F given intramuscularly to normal men. They observed eosinopenia and lymphocytopenia, negative nitrogen balance, lowered renal threshold for glucose, loss of potassium, and retention of sodium and chloride. They suggested that, since Compound F reproduces the electrolyte changes characteristically produced by ACTH, there appeared no need to postulate a separate DCA-like substance as being liberated by the adrenal in response to ACTH. Conn, Louis & Fajans (79) performed extensive metabolic studies on a normal young woman given 400 mg. per day of either free Compound F or Compound F acetate, each orally and intramuscularly (4 separate experiments). Intense metabolic effects were observed when either the free compound or the acetate was given orally or when the free compound was given intramuscularly. However, Compound F acetate administered intramuscularly produced only minor metabolic effects. The intensity and diversity of the metabolic effects of Compound F (including sharp increases in both urinary 17-ketosteroids and formaldehydogenic steroids) were such as to be indistinguishable from those observed after large doses of ACTH. The authors suggest that Compound F may well be the steroid secreted by the normal adrenal cortex when it is stimulated by ACTH. Perera *et al.* (98) observed a lesser effect of Compound F than of Compound E on electrolyte metabolism in man. Inasmuch as Compound F acetate was given intramuscularly in these experiments the discrepancy is explainable (79).

Green *et al.* (99) found that the influence of desoxycorticosterone glucoside upon renal tubular reabsorption of sodium is dependent largely upon the sodium load presented. Perera & Ragan (100) suggest that, since increased intake of sodium fails to raise blood pressure in hypertensive vascular disease associated with Addison's disease until DCA or cortisone are supplied, the pressor effect of sodium is connected in some way with the metabolism of the adrenal steroids. Perera (101) states that cortisone seldom increases blood pressure unless renal damage exists.

Woodbury *et al.* (102), measuring brain excitability in the adrenalectomized rat by means of the electric shock seizure threshold, find that cortisone or adrenal cortical extract antagonize the effect of DCA on brain excitability. They conclude that in the absence of an intact pituitary-adrenal system this phenomenon probably represents direct competition between cortisone and DCA for a strategic locus within the cell. Friedman *et al.* (103) observed that DCA failed to prevent the suppression of growth of immature rats which is produced by cortisone, and that, although the elevation of blood pressure

which usually follows administration of DCA did not occur in the presence of cortisone activity, nevertheless, cortisone failed to prevent the DCA-induced increase in weight of the heart and kidneys. These findings are interpreted as indicating that cortisone cannot be considered antagonistic to the cardiovascular renal effects of DCA.

Circulating eosinophils.—Fisher (104) and Best (105) and their associates observed a sufficiently broad physiological range and sufficiently great diurnal variations in eosinophil counts in normal people as to make hazardous interpretations of test procedures based upon their change. Several groups (69, 106, 107, 108) have observed in patients with Addison's disease a significant decrease of blood eosinophils following a test dose of epinephrine whereas the same patients exhibited no eosinopenia following ACTH. Broch & Haugen (109) conclude that the effect of epinephrine on circulating eosinophils in normal men is too variable to serve as a useful clinical test for function of the adrenal cortex. Ferguson (110) observed no significant differences in baseline eosinophil counts or in the 4-hr. epinephrine tests in normal, pregnant, and pre-eclamptic women. He found, too, that disappearance of circulating eosinophils in eclampsia is not constant. Perlmutter & Mufson (111) note that the eosinopenic response to hypoglycemia produced by intravenous insulin is much more constant than it is to epinephrine, providing the blood sugar level falls below 35 mg. per cent. In four patients with Addison's disease and one with hypopituitarism, this test failed to provoke eosinopenia. Bliss *et al.* (112) report that 2 mg. of epinephrine in oil given intramuscularly four times daily provokes a sharp increase in adrenocortical function in man as evaluated by the rise of 17-ketosteroids and the eosinopenic response.

In rats McDermott *et al.* (2) found that the initial increase in eosinophils following either administered epinephrine or the release of endogenous epinephrine is dependent on the contraction of the spleen. By correlating the fall in adrenal ascorbic acid with the eosinopenic response, they conclude that the latter is an accurate and satisfactory index of release of cortical steroids. However, they find no evidence that the initial level of blood eosinophils bears any constant relation to the functional capacity of the gland. Spain & Thalheimer (113) observed a sufficient accumulation of eosinophils in the spleen of mice 8 hr. after administration of cortisone to account for the number that had disappeared from the blood. That the spleen, however, is not required for the eosinopenic response is evident from the work of McDermott *et al.* (2) and Renold *et al.* (33). Rosenberg & Lewis (114) established a relationship in adrenalectomized mice between the degree of eosinopenia and the amount of cortisone administered. They then assayed from the urine of normal men eosinopenogenic material. A great increase of such material was obtained when the men were given small doses of either ACTH or cortisone.

Electrolyte composition of sweat and saliva.—Locke *et al.* (115) have confirmed earlier work indicating that under standard conditions the electrolyte composition of thermal sweat reflects the degree of activity of the adrenal cortex with respect to its electrolyte regulating activities. They have delin-

eated several nonendocrine factors which must be controlled if sweat composition is to be reliable as an indicator of cortical activity and have evolved a more refined index (the sweat-chloride-rate index). The test reflects clearly changes in steroidal activity when normal men are given either DCA or ACTH. Of four patients studied with essential hypertension, two exhibited an index indicative of excessive adrenocortical activity. Davies & Clark (116) report a group of "endocrine hypertensive" patients characterized by obesity of the trunk, hirsutism, and menstrual irregularities (Schroeder's pseudo-Cushing's syndrome) whose sweat sodium concentrations indicated excessive cortical activity. Other patients with hypertension showed sweat sodium values which fell in the normal range. Eisenberg *et al.* (117) found no difference in sweat sodium concentrations in hypertensive and normotensive people. In an effort to overcome some of the difficulties attending collection of samples of sweat, Frawley and Thorn (118) studied the sodium-potassium ratio of saliva. They observed that under standard conditions of collection of the sample, the salivary sodium-potassium ratio affords a simple means of following changes in adrenal cortical activity with respect to electrolyte regulation.

Carbohydrate metabolism.—During the year, a number of reports have appeared dealing either directly or indirectly with effects of ACTH and adrenosteroidal compounds upon the metabolism of carbohydrate. Segaloff & Many (119), employing phloridzinized rats, observed that ACTH as well as Compounds A, B, E, and F increased glycosuria and ketonuria considerably in excess of what could be accounted for on the basis of the accompanying increase in nitrogen excretion. They conclude that the rat is capable of deriving glucose from fat as well as from protein. Aboud & Kocsis (120) found that the decreased ability of hypophysectomized rats to synthesize glycogen from glucose was restored to normal by ACTH; and that the decrease in anaerobic glycolysis exhibited by the brain of hypophysectomized animals was also restored to normal by ACTH. Engel & Scott (121) observed that adrenocortical steroids are related in some way to the capacity of the adipose tissue in the dorsal interscapular fat pad of the rat to synthesize glycogen. Albaum *et al.* (122) observed no significant change in rat muscle phosphocreatine or adenosinetriphosphate content as the result of adrenalectomy or treatment with cortisone. Gemzell & Samuels (123) found no change in the concentration of phosphates in the tissues of the rat as the result of hypophysectomy but observed a reduced rate of turnover of inorganic phosphate between cells and extracellular fluid which was promptly increased upon administration of ACTH. Nichols & Gardner (124) administered 1,1-dichloro-2,2-bis-(chlorophenyl)-ethane (DDD) orally to dogs over prolonged intervals and found atrophy of the fascicular and reticular layers of the adrenal cortex. Such animals are unusually sensitive to insulin but show no evidence of electrolyte imbalance. Since the morphological and physiological results are similar to those obtaining after hypophysectomy it was suggested that the drug may block the action of endogenous ACTH in the dog.

Several more observations have been reported which relate to glycosuria

or hyperglycemia in man as produced or influenced by ACTH or adreno-corticoids. Mazar & Bogdasarian (125) observed no intensification of the diabetic state of a patient given small doses of ACTH for the treatment of keratitis. With large doses of ACTH, however, Fajans *et al.* (126) produced tremendous intensification of the diabetic status associated with great insulin resistance in a diabetic treated for leukemia. Soffer *et al.* (127) noted the onset of diabetes mellitus after 18 days of cortisone and 3 days of ACTH in a patient with a strong family history of diabetes. Bunim (128) reported the development of diabetes in a patient with no family history of diabetes. After a 60-day course of cortisone the glucose tolerance curve did not return to normal for six weeks. Sprague *et al.* (67) quote the case of a patient who, without previously known diabetes or family history of diabetes, developed severe diabetic acidosis while receiving large doses of cortisone and ACTH. Green *et al.* (129) observed marked improvement in the severity of diabetes following bilateral adrenalectomy in a patient with malignant hypertension and diabetes. The insulin requirement was proportional to the amount of cortical extract administered. Brown *et al.* (130) treated three diabetic patients with coexisting rheumatoid arthritis with either ACTH or cortisone. Since the arthritis was relieved as the metabolic aberrations worsened and since similar intensification of the diabetic status by withdrawal of insulin in the absence of ACTH or cortisone gave no antiarthritic effect, they concluded that the gross metabolic effects of these substances cannot be correlated with their antiarthritic properties. As has been observed previously, Dustan *et al.* (131) determined a decrease in maximum renal tubular reabsorptive capacity for glucose during and for some time following administration of either ACTH or cortisone. Adrenal cortical function studies carried out in diabetic patients by Wilson *et al.* (132) indicate no evidence that adrenal cortical hyperfunction is a factor in maintaining the hyperglycemia of diabetes mellitus. In fact, Field & Marble (133) report that, as measured by the eosinopenic response to surgical stress, diabetics, as a group, exhibit diminished adrenal cortical function. Conn *et al.* (79, 96) have reported that both Compound F and Compound B reduce carbohydrate tolerance in man, the former steroid being more effective in this regard than the latter.

Glutathione of blood.—Hess *et al.* (134) have confirmed earlier observations that administration of ACTH in man results in a fall of reduced glutathione of blood. In addition, they found that total glutathione of blood did not decrease. A correlation was found between the degree of fall of reduced glutathione and the intensity of hyperglycemia produced by ACTH. Lazarow (135) observed that cortisone-induced diabetes in the rat is associated with a decrease of blood reduced glutathione. However, administration of reduced glutathione to such animals resulted in a sharp increase of glycosuria. He suggests that glutathione may protect cortisone from destruction by oxidation and thus potentiate its diabetogenic effect. Henneman & Altschule (136) observed in psychotic patients that within 2 to 4 hr. after administration of epinephrine or ACTH, or following electric or insulin shock, blood reduced glutathione increased. Ingbar *et al.* (137) gave rats sufficient ACTH

for 3 to 10 days to produce sustained eosinopenia. They observed no change in blood glutathione but found a decrease in the nonprotein sulfhydryl content of kidney and an increase of it in liver tissue. In an effort to discover a physiological system which would reflect changes in sulfhydryl concentration induced by cortisone, Anderson *et al.* (138) studied the inhibitory effect of cortisone upon the skin-spreading phenomenon produced by injected hyaluronidase. They showed clearly that administration of reduced glutathione reverses the inhibitory effect of cortisone on this phenomenon and suggest that cortisone may produce this inhibitory effect by reducing the available sulfhydryl groups.

Purine metabolism.—Fajans *et al.* (139) studying ACTH-induced changes in purine and carbohydrate metabolism in both Dalmatian and mongrel dogs concluded that increased production as well as increased renal clearance of purines accounts for the increase in urinary excretion of these substances during administration of ACTH. In mongrel dogs the predominant increase was of allantoin, while in the Dalmatians it was predominantly uric acid which increased. A relationship exists between the ACTH-induced increase of urinary uric acid and the diabetic response. Using isotopic uric acid in a patient with gout and in a normal subject, Benedict *et al.* (140) find little evidence that ACTH increases production of uric acid and conclude that increased renal clearance of uric acid accounts for ACTH-induced uricosuria. The same conclusion was made by Friedman & Byers (141) in their study on rats.

Lipid metabolism.—Three groups of investigators (142, 143, 144) report upon the production in rabbits of intense lipemia and fatty livers by the administration of either ACTH or cortisone. Levin & Farber (145) working with adrenalectomized mice found that neither cortisone nor pituitary extract would produce fatty livers, but pretreatment with cortisone allowed the pituitary extract to become effective in mobilizing fat from the depots to the liver. They believe the pituitary factor is as yet unidentified. In a study of lipogenesis from carbohydrate, by determining uptake of deuterium into liver and carcass fat by female rats on a high carbohydrate, fat-free diet, Welt & Wilhelmi (146) concluded that adrenalectomy is followed by an increased rate of lipogenesis from carbohydrate, and that the adrenalectomized animal tends to utilize a greater proportion of carbohydrate over the pathway of fat synthesis and oxidation. They found too that activation of the adrenal cortex or administration of growth hormone inhibits greatly the process of lipogenesis from carbohydrate. Altman *et al.* (147) studying lipogenesis in the perfused rat liver with C^{14} acetate found that cortisone plus insulin added to the perfusion blood enhanced greatly the synthesis of fatty acid without affecting cholesterol synthesis, but cortisone alone produced a twofold increase in the C^{14} recovered in cholesterol. Using the incorporation of P^{32} into liver phospholipid as the index, Geschwind, Li & Evans (148) observed that hypophysectomy results in a decreased turnover of liver phospholipid, and that either ACTH or growth hormone increase it but not to normal. Zilversmit *et al.* (149) found that, although dogs suffering from complete adrenal insufficiency showed no consistent

changes in plasma phospholipids, adrenalectomized dogs maintained on DCA exhibited a great decrease in plasma phospholipid concentration, total circulating plasma phospholipid, and plasma phospholipid-protein ratio. Geyer *et al.* (150) noted that the recently hypophysectomized rat can utilize lipids (octanoic acid) normally but that long-standing hypophysectomy results in decreased utilization of the lipid.

Kinsell *et al.* (151, 152) observed that either ACTH or cortisone administered to man during a standard three-and-one-half-day fast results in a major diminution or suppression of fasting-induced hyperketonemia. They conclude that adrenal steroids may accelerate the rate of ketolysis but may also decrease ketone formation by modifying the catabolic pathway of fatty acids. Fajans *et al.* (126) gave a diabetic patient large amounts of ACTH over a prolonged period of time and came to the conclusion that under these circumstances ACTH appeared to either increase ketolysis or decrease ketogenesis. Adlersberg *et al.* (153, 154, 155) studied the serum lipid partition in patients, suffering from a variety of conditions, who were being treated with either ACTH or cortisone. With cortisone, they observed a gradual increase of total and esterified cholesterol as well as of phospholipid but a sharp decrease of serum neutral fat. With ACTH there occurred a decrease of cholesterol during the first 6 to 15 days followed by a rise. The phospholipid fraction did not change significantly while neutral fat fell sharply from the sixth to the twentieth day and then returned slowly toward baseline values.

RELATION OF THE PITUITARY-ADRENAL SYSTEM TO OTHER ENDOCRINE GLANDS

Thyroid.—Long standing hypothyroidism results in decreased adrenocortical function. It is evident, too, that adrenal hyperactivity is capable of diminishing function of the thyroid gland. Maqsood (157), Kowalewski & Bastenie (158), Freedman & Gordon (159), and Vieillard & Perloff (160) have observed evidence of decreased adrenocortical activity in mice and rats as the result of thyroidectomy or the administration of either anti-thyroid drugs or radio-iodine. The adrenals become smaller, 17-ketosteroids diminish in female rats, and the eosinopenic response to ACTH or epinephrine is decreased. Where attempted, the administration of thyroxin has reverted the adrenal gland and its function to normal. Gabrilove & Soffer (161), however, report a normal adrenal ascorbic acid response to ACTH or epinephrine in rats treated with propylthiouracil, despite the adrenocortical involution. Statland & Lerman (162) observe that in recently developed myxedema, adrenal cortical function may be normal, but in many cases of primary myxedema there is secondary depression of cortical functions.

Money *et al.* (163) found that thyroid weight and iodine uptake diminished in rats treated with ACTH, cortisone, or epinephrine but not with DCA, Compound S, or adrenal cortical extract. Investigations on man by Hardy (164), Hill (165), and Wolfson (166) and their respective associates indicate that continued administration of either ACTH or cortisone results in a decreased uptake of I^{131} and a diminished concentration of serum pro-

tein bound iodine. Because adrenocorticoids appear to be calorigenic *per se* (165, 166), measurements of oxygen consumption may not disclose the existence of deficient thyroid function. It seems likely that adrenocortical hormone depresses pituitary elaboration of thyrotropic hormone, since administration of the latter in the presence of a high level of adrenal steroid restores toward normal the uptake of I^{131} and the level of serum protein bound iodine (165). Wolfson (166) suggests that corticogenic hypothyroidism is the chief cause of the hypercholesterolemia which appears after prolonged treatment with ACTH and cortisone [Adlersberg *et al.* (153, 154, 155)]. A sharp increase in renal excretion of iodine following surgical operations in man was observed by Gemmell & Perry (167). Since they were unable to reproduce the phenomenon by administration of ACTH, they concluded that it was not due to increased adrenocortical activity and suggested that it could result from increased mobilization of thyroid hormone and its rapid breakdown in peripheral tissues.

Posterior pituitary.—Birnie and his co-workers (168) report that the antidiuretic substance present in the blood of intact rats, but absent after hypophysectomy, increases in the blood of adrenalectomized animals. It can be depressed by giving saline, DCA, or adrenal cortical extract. Large doses of corticoids do not reduce the amounts present in the blood of normal rats. Nagareda & Gaunt (169) postulate that integration between posterior pituitary and adrenal cortical activity may be achieved in the hydrated state by the responsiveness of both glands in a converse manner to changes in the osmotic pressure of plasma.

Gonads.—McDermott *et al.* (2) found that the eosinopenic response to epinephrine observed in totally adrenalectomized male rats was not observed in male rats that were simultaneously adrenalectomized and gonadectomized. They suggest either an overlap in the effects of adrenal and gonadal steroids or stimulation by ACTH of adrenal cell rests in the testes.

URINARY EXCRETORY PRODUCTS OF STEROIDAL METABOLISM

It seems to the reviewers that insufficient attention has been given to the proposition that there exists a vast difference between steroidal materials which leave the adrenal via the adrenal vein and those which are found as degraded and metabolized end products in the urine. Relationships between them that normally may exist under one set of conditions may not hold true under another. Interconversions of steroidal compounds and pathways of steroid metabolism may be profoundly altered in the presence of either disease or a change in the metabolic state. Until the answers to such basic problems are available it will remain impossible to conclude that isolation of a given compound from urine represents synthesis by the adrenal of an unusual steroidal compound.

Polley & Mason (170) observed rather striking differences among individuals in the urinary excretions of 11,17-oxysteroids and 17-ketosteroids which followed administration of Compound S intramuscularly. Landau *et al.* (171) found that, following stimulation of the cortex with ACTH, the rise of urinary dehydroisoandrosterone was parallel to that of total

17-ketosteroids. No increase of dehydroisoandrosterone occurred when urinary 17-ketosteroids rose in response to testicular stimulation with chorionic gonadotropin or when testosterone or cortisone were given. Increase of urinary dehydroisoandrosterone appeared to reflect increased adrenocortical activity. Dobriner *et al.* (172, 173) could find no increase in 11-desoxysteroids in the urine of man following administration of large amounts of cortisone but did find an increase in 11-oxysteroids. Since administration of an 11-oxysteroid does not result in increased amounts of 11-desoxysteroids in the urine, but administration of ACTH increases both the urinary 11-desoxy and 11-oxysteroids, they conclude that the human adrenal cortex produces both types of steroids. When they (173) administered isotopically labelled C 21 steroid hormones of the 11-desoxy type their transformation to C 19-17-ketosteroids was observed. This they feel constitutes proof that adrenal cortical 11-desoxy-precursors contribute to urinary androsterone and etiocholanolone. Pincus *et al.* (174) studied the metabolic effects of oral versus intramuscular cortisone in arthritic and schizophrenic patients. There was considerable divergence of the metabolic effect by the two routes. Since oral administration led to an increase and intramuscular administration to a decrease of urinary 17-ketosteroids, it was postulated that oral cortisone may be oxidized in the liver to produce a large percentage of 17-ketosteroid catabolites which are metabolically inert.

Liver disease.—Eisenberg *et al.* (175) found that in both males and females with chronic liver disease, 17-ketosteroid excretion was considerably below the normal range. Zarrow, Munson & Salter (176) observed that in males with liver disease the ratio of urinary androgen (biologically determined) to total 17-ketosteroids is considerably lower than in normal or in hypogonad males. Butt *et al.* (177) studied two patients with liver disease who had low levels of urinary 17-ketosteroids and normal levels of 11,17-oxysteroids. Administration of large amounts of cortisone depressed 17-ketosteroid excretion to zero and increased the amount of 11,17-oxysteroid in the urine. They concluded that the damaged liver cannot convert adrenal precursors to 17-ketosteroids effectively. Bongiovanni & Eisenmenger (178, 179) report that patients with chronic liver disease have a depressed excretion of 17-ketosteroids and an elevated excretion of corticoids. As compared with normals, patients with liver disease excrete only a small proportion of the 17-ketosteroids as glucuronidates. Upon administration of ACTH both the corticoids and the 17-ketosteroids rise, a much greater proportion of the latter being found as the glucuronidates.

ADRENAL FUNCTION IN INFANCY AND OLD AGE

In Moore's (180) recent review, he states with respect to adrenal function in embryonic life:

Evidence for a definite function on the part of the x-zone, or the more generalized cortex, appears to be lacking despite the quantity of speculation on the subject. This is not to say that the embryonic adrenal has no function, but merely to express the opinion that a definite functional role is yet to be established.

Jailer *et al.* (181) and White & Sutton (182) find that epinephrine does not produce a significant eosinopenia in premature infants before the ninth day of age, whereas the majority of full term infants react promptly in the first 24 hr. of life. Both types of infants exhibit an eosinopenic response to ACTH as early as the second or third day of life (181). Read *et al.* (183) and Klein (184, 185) agree that responsiveness of the adrenals of newborn infants to stimulation with ACTH is significantly greater in the second than in the first week of life. Kowalewski (186) finds a progressive diminution of urinary 17-ketosteroids with advancing age in both males and females. Solomon & Shock (187) observed no difference between young and old men with respect to eosinopenia following administration of ACTH. The much greater eosinopenia after epinephrine in the young than in the aged suggested that the aged secrete less ACTH in response to epinephrine. Bonner *et al.* (188) observed a poor eosinopenic response to ACTH in aged, debilitated subjects, but a better one in aged, debilitated subjects suffering from cancer. Pincus (189) compared the response to various forms of adrenocortical activation in younger (median age 32) and older (median age 77) men. He concluded that men in good health, though aged, may preserve relatively intact the pituitary-adrenal mechanism involved in the response to acute stress.

SPECIFIC DEFICIENCY STATES AND ADRENO-CORTICAL FUNCTION

Banerjee & Deb (190) report decreased concentrations of both ascorbic acid and cholesterol in the adrenals of scorbutic guinea pigs. Oesterling & Long (191) agree that this is true in late scurvy but find that, in early scurvy, adrenal cholesterol is higher than in normal controls, despite a 95 per cent depletion of adrenal ascorbic acid. At this stage, ACTH administration produces a 42 per cent reduction of adrenal cholesterol with no further reduction of ascorbic acid. Hyman *et al.* (192) find, too, that deficiency of adrenal ascorbic acid in guinea pigs does not interfere appreciably with the capacity of the gland to respond to ACTH. Treager *et al.* (193) observed a normal eosinopenic response to ACTH in five patients suffering from clinical scurvy.

In pyridoxine deficiency the same changes in the production of leukocytes occur in both intact and in adrenalectomized mice [Mueller, Weir & Heinle (194)]; therefore, the changes cannot be attributed to an adrenocortical response to stress. Melampy *et al.* (195) find that pantothenic acid deficiency in mice leads to lymphopenia followed by lymphocytosis, hypertrophy of the adrenal zona fasciculata with depletion of lipid material, atrophy of the thymus, and splenic enlargement. Handler & Berheim (196, 197) on the basis of experiments in partially nephrectomized, hypertensive rats suggest that either choline deficiency or protein deficiency may decrease synthesis of ACTH. Handler & Georgiade (198) observed that rats fed a low protein diet for 10 weeks were unable to avoid hypoglycemia during a subsequent fast, but that administration of ACTH corrected the defect. They suggest the possibility of functional hypopituitarism as the result of protein deprivation.

DETECTION OF ACTH IN TISSUES

Ferrebee *et al.* (199) present evidence that ACTH and insulin can be labelled with I^{131} without interfering with their hormonal activities. Sonenberg and associates (200, 201), on the basis of radio-autographs of tissues shortly following administration of ACTH labelled with I^{131} , conclude that the adrenal cortex possesses a specific binding capacity for ACTH. Richards & Sayers (202) injected rat ACTH into rats intravenously and found that it disappeared rapidly from the blood in either intact or in adrenalectomized rats. In intact rats, at 5 min. after injection, 40 per cent of the injected dose was in the extracellular fluid and 20 per cent was fixed in the kidneys; at 15 min., a negligible amount remained in the extracellular fluid and 15 per cent was found in the kidneys. A very small quantity was detected in the adrenals and none in the liver or urine. Van Dyke *et al.* (203), using data from parabiotic rats, calculated that the ACTH space of the rat body is equivalent to 43 per cent of the body weight and that the average life of the circulating ACTH molecule in the rat is approximately 17 min. Bornstein & Trehwella (204) prepared acetone extracts of 6 cc. of plasma from normal and abnormal individuals. Assays by the adrenal ascorbic acid depletion method suggested ACTH-like activity in normals to be in the range of 197 μ g. per 100 cc. of plasma, with higher values in Cushing's syndrome and lower ones in Simmonds' disease. The level was normal in uncontrolled diabetes without ketosis. With respect to such evaluations by assay procedures, the recent study by Reinhardt & Li (205) is important. They tested five types of preparations of ACTH (proteins and peptides) by the adrenal ascorbic acid depletion method, by the adrenal weight maintenance test, and by the secondarily manifested effects upon thymus and lymph nodes. Some of the preparations with great ascorbic acid depleting activity were weak in adrenal weight maintenance and vice versa. The one with the greatest value for adrenal ascorbic depletion was the least active in reducing the weight of the thymus. Many questions are raised by these results including the one suggested by Young (77) that perhaps there exist more than one ACTH.

OTHER OBSERVATIONS

Castor & Baker (206) found that local application of adrenal cortical hormones to the skin of rats produced local modification of the histology of the skin, namely, a thinner dermis and epidermis, cessation of hair growth, smaller sebaceous glands, loss of collagenous fibers, and fewer fibroblasts. After 160 days of such treatment the skin became refractory and despite further applications returned to normal. They suggest that capacity to develop refractoriness is probably an attribute of peripheral tissues. Jailer & Knowlton (207) observed a return to normal values of 17-ketosteroids and neutral reducing substances of the urine in an Addisonian during the latter part of pregnancy. She was maintained with DCA throughout the pregnancy. During the period of normal excretory levels of steroids, eosinopenia could be produced by either ACTH or epinephrine. All of these phenomena reverted to the true Addisonian status one week after parturition, and the

urine of the newborn male infant contained only traces of steroidal material. ACTH-like activity was found in the crude extract of the placenta. It appeared that the placenta had been capable of producing both adrenocortical-like and ACTH-like hormones. Paschkis *et al.* (208), using the Venning mouse liver glycogen assay method, have been able to detect changes in adrenocortical hormone levels in the peripheral arterial blood of dogs subjected to a number of stressing circumstances. Pretreatment of intact rats with ascorbic acid prevents the eosinopenia and the histological depletion of adrenal steroids which ordinarily follows administration of epinephrine (209), and it also delays the eosinophilia which characteristically follows administration of epinephrine in the adrenalectomized rat (210).

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THYROID GLAND

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Some 3,000 publications relating to the thyroid have been collected during the interval July, 1950, to July, 1951. Merely listing this tremendous bibliography would require space six times greater than that allotted for this review. Because of this and because the editors requested a summary colored by the reviewer's personal leanings, the author has selected only a small portion of material which was of especial interest to him or which caught his fancy for one or another reason. Several excellent summaries dealing with the thyroid comprehensively (1, 2), or with some restricted aspect of it [anti-thyroid compounds (3), iodine in nutrition (4), radioiodine (5), chemistry of thyroglobulin (6)] may be consulted.

PRODUCTION OF THYROID HORMONE

Since most of the recent work on the thyroid was performed with radioiodine (I^{131}), a statement concerning the iodine cycle seems necessary. A multiplicity of events occurs following the administration of radioiodine. During equilibration with the iodide space, part of I^{131} is being removed by the kidneys and the thyroid. The radioiodine excreted via the kidneys is lost to the body, but the labeled iodine accumulated by the thyroid is synthesized into thyroid hormone. After a finite but variable period of time, radioactive hormone is being secreted into the circulation. Circulating thyroid hormone diffuses into the thyroxine space, and is utilized in the tissues. Some of the radioactive atoms of iodine liberated return to the general iodide pool while some of the administered I^{131} is still being removed by the kidneys and thyroid. Consequently, at any time following the injection of radioiodine, a number of events is taking place simultaneously. Some radioatoms of iodine have completed one cycle and are entering a second while some have not completed a single cycle. For the purposes of clarity, however, each phase will be discussed separately.

Extrathyroidal metabolism of iodide.—After administration of radioiodine, measurements of the concentration of I^{131} in the blood, and in the thyroid and urine, can be utilized to determine the iodide space. In man, the iodide space, defined as the amount of I^{131} remaining in the body divided by the percentage of dose per liter of plasma, is about 18 l. at 1 hr. (7). It increases slowly to 25 l. (40 per cent body weight) at the end of 6 hr. The diffusion space for iodide is greater in patients with thyrotoxicosis than in normal persons. Iodide space is theoretic, not real, since it is defined as a volume containing the total store of iodide in the same concentration as found in serum. That such is not the case is indicated by the finding that gastric juice contains radioiodide in a concentration 40 times and salivary juice 30 times greater than

that of plasma. However, the curves of disappearance of radioiodide from salivary and gastric juices follow in parallel fashion the curves of disappearance of I^{131} from plasma (7). Animal investigation (8) has likewise indicated that radioiodide is found in the stomach and small bowel at higher concentrations than in the thyroid during the first 6 hr. The concentration in the gastrointestinal tract declines with the fall of I^{131} in the blood, while the concentration in the thyroid continues to rise. Radioiodide is also present in cerebrospinal, ascitic, and edema fluid (7), and is transported across the placenta and secreted in milk (9).

Radioiodide diffuses freely into the red blood cells (10). The concentration of I^{131} in erythrocytes is two-thirds that of plasma. The cell to serum ratios at various intervals of time following the administration of iodide in the rat were fairly constant, indicating that rapid adjustments of iodide concentration between erythrocyte and plasma occur (11). While radioiodide approaches equilibrium with its diffusion volume, it is being removed by the thyroid and kidneys. In the human, at the end of 6 hr., the thyroid will contain about 25 per cent, the urine 40 per cent, and remainder of the body about 35 per cent of the dose (7). The kinetics of the urinary excretion of iodide have been discussed in excellent detail, and methods for the determination of renal clearance have been given (12). The renal clearance is about 32 ml. per min. for both normal and hyperthyroid persons. Allowing for the erythrocyte I^{131} , the clearance is about 37 ml. of blood per min. Since renal blood flow is 1,200 ml. per min., the efficiency of iodide removal is roughly 3 per cent (7). Renal clearance is depressed in myxedema and in patients with various types of renal disease (12). It is also markedly diminished following hypophysectomy (13). Eventually, virtually all the radioiodide not collected by the thyroid is excreted in the urine, except for a small percentage lost in the feces, sweat, or expectorate. The fate of iodine atoms in the thyroid may now be followed.

Iodide trap.—The selective affinity of the thyroid for iodide has been referred to as the "iodide trap" and represents a mechanism by which inorganic iodide is held in the thyroid at a concentration many times greater than that in plasma. The trapped iodine is diffusible. Thus, it is incorrect to speak of iodide trapped in the thyroid at, say, 4 hr. following a tracer dose, since at this time the iodide is held not only as trapped iodide but also as organically bound iodine. An excellent study (14) of the trapping mechanism has been made in rats. After the biosynthetic function was blocked by anti-thyroid drugs, the concentrating power of the trap (thyroid I^{131} /plasma I^{131}) was of the order of 250:1. Subsequent to hypophysectomy, this ratio falls to one-tenth of the preoperative value. It is restored in part by the administration of thyrotropin. The diminished trapping ability of the thyroid after hypophysectomy is not related to the change in cellularity of the gland or to the decrease in weight. A characteristic property of the iodide trap is that iodide held by the thyroid is almost completely discharged following the administration of potassium thiocyanate. The mechanism of this action is not clear. The thyroid concentrates potassium thiocyanate, but only 1 per cent

as effectively as it concentrates iodide (15). Furthermore, the accumulation of potassium thiocyanate is not increased in hyperplastic conditions, although the iodide uptake is markedly augmented. The comparative trapping of elements of the seventh periodic group has been compared with that of iodide given simultaneously (16). Thus Re^{186} was concentrated from 60 to 200 times more than Br^{82} , and about equal to I^{131} . The fundamental nature of the iodide trap remains unsolved. The concentrating mechanism may involve a specific enzymatic system capable of holding iodide in diffusible form or some very special protein which selectively binds iodide ions. The iodide is held in the trap for a brief period of time. Progressively more and more radioatoms of iodide are removed from the trap and organically bound within thyroglobulin.

Biosynthesis.—Over a period of 24 to 48 hr., the accumulation of I^{131} by the thyroid proceeds in an orderly fashion, analysis of which has received considerable attention (7, 17). Since the I^{131} is effectively removed from the body for some time by being organically bound, thyroïdal clearance of iodide can be ascertained. For euthyroid persons, the clearance is 25 ml. per min., and for hyperthyroid patients, from 3 to 10 or more times greater (7). Thus the determination of thyroïdal iodine clearance appears to be one of the better methods for diagnostic use. It is also evident that, since the thyroid clears a constant volume of plasma, the uptake of I^{131} by the thyroid will be proportional to the plasma concentration of I^{131} , which in turn is dependent on the size of the diffusion space for iodide and on the renal clearance. The thyroïdal collection of I^{131} is decreased by hypophysectomy (18) to 10 per cent of preoperative value and restored at least in part by the administration of thyrotropin. Moreover, the rate of organic binding of I^{131} in hypophysectomized animals is slower than normal, but eventually 95 per cent of the thyroïdal I^{131} becomes organically bound (19). Curves depicting the proportions of acid-soluble and acid-insoluble thyroïdal iodine at varying intervals in hypophysectomized rats show that the rate of conversion of diiodotyrosine to thyroxine is only a fraction of that of normal animals.

Chemical investigation disclosed that monoiodotyrosine is present in the thyroid (rats, chicks, and sheep) and accounted for 15 to 20 per cent of the acid-soluble iodine, thus constituting a precursor in the biosynthetic production of thyroxine (20). The thyroid, in addition, contains iodide, monoiodohistidine (21), diiodotyrosine, thyroxine, thyroglobulin, possibly elemental iodine, and at least three other iodinated compounds (22), the chemical nature of which is unknown. Furthermore, the proportion of some of these compounds changes with time following the injection of I^{131} . Thus, intra-thyroidal metabolism of iodine is more complicated than has hitherto been imagined. The progressive accumulation of free thyroxine, even though constituting only 1 per cent of the total I^{131} of the thyroid, makes it appear that thyroxine is removed somehow from thyroglobulin preparatory to its release into the circulation. The exact mechanism by which thyroxine is preferentially split from thyroglobulin is not known. A proteolytic thyroglobulinase has not been unequivocally demonstrated. An interesting and important

intermediary process involves the deiodination of diiodotyrosine by a thyroidal enzyme, desiodase, during which the liberated iodide is returned to the iodide pool within the gland for reincorporation into thyroglobulin (23). The virtual absence of diiodotyrosine from the blood has been attributed to this process but, as will be pointed out later, there is another reason which explains the absence of this amino acid from the blood. The entire biochemistry of hormonal synthesis is still in need of intensive work. In spite of the disputed status of thyroglobulinase, reports of other types of enzymatic activity of thyroid tissue continue to appear. A proteolytic enzyme liberating tyrosine from hemoglobin (24), an alkaline glycerophosphatase (25), and an enzyme with mucolytic activity (26) have been reported. It is intriguing that the mucolytic activity of the thyroid is increased by thyrotropin and decreased by administration of iodide. The glycoprotein fraction of the thyroid and the mucolytic activity may be significant in the regulation of the viscosity of the colloid (27).

Hormonal release.—The secretion of free thyroxine into the blood appears to be by simple diffusion, since the concentration gradient of free thyroxine between gland and plasma is about 100:1. The liberation of hormone may be followed by means of radioactive iodine. The secretory rate, as determined by the reduction in radioactivity over the gland, is in error to the extent that some radioiodide has entered the thyroid during the same interval that thyroxine I^{131} has left. Therefore, the true secretory rate will be higher by some fraction than the observed speed of thyroidal I^{131} loss. In rats, it has been shown that the rate of biologic decay of thyroidal radioiodine expressed as a proportional rate (28) (per cent per day) or as in terms of half-life (29) reflects the release of hormone from the gland. The uncorrected secretory rate of rats maintained on an iodine-deficient diet is about 10 per cent per day, which corresponds to the discharge of about 2.5 μ g. L-thyroxine per day. This rate is reduced by hypophysectomy (30) to about 1 per cent per day, increased by the administration of thiouracil (50 per cent per day), and inhibited by thyroxine (31). Iodide had no constant effect on the rate, whereas thyrotropic hormone greatly augmented it.

It is fairly obvious that this method can be utilized for the assay of thyroid material (32), thyrotropic hormone, and goitrogenic compounds, and for any study involving experimental alteration of the endogenous rate of hormonal liberation. However, some complexities are present, since it was found that large doses of thyroxine did not suppress hormonal secretion in the chick as effectually as small doses (33). It was suggested that nonthyroxine I^{131} may be secreted by the thyroids of normal and thyroxine-treated animals. Various attempts to utilize the hormonal secretion rate as a clinically useful diagnostic test have been made, on the general proposition that such a determination would be the most significant indication of thyroidal function. The amount of L-thyroxine in milligrams secreted from the gland per day in various thyroid disorders has been calculated from *in vivo* counts over the thyroid and designated as the "thyroid metabolic rate" (34). This

is a confusing term, and the mathematical transformation utilized is not immediately evident.

The secretion rate of thyroidal hormone continues to be investigated by the classic method of inhibition of goitrogenic action. It was found to be 18 μ g. thyroxine per day by the first week of life in the white Pekin duck, correlating with the high rate of growth of this fowl (35, 36). In a fast-feathering strain of chicks the rate of liberation of thyroxine was found to be slightly higher than in a slow-feathering strain of the same species (37).

Circulating hormone.—That the circulating thyroid hormone is thyroxine has received additional confirmation on the basis of isotope dilution techniques and paper chromatography. Twenty-four hr. subsequent to administration of I^{131} , iodide and thyroxine have been identified in the blood (38). Radiomonoiodotyrosine and radiodiiodotyrosine have not been found in the blood; but a third as yet unidentified compound, different from any present in the thyroid, has been observed (22). In euthyroid and hyperthyroid persons, the protein-bound I^{131} has been identified largely, if not entirely, as thyroxine (39, 40). In general, most investigators are agreed that the major portion of what is known as protein-bound iodine of serum is thyroxine, although the possibility that it may be a small peptide of thyroxine is still not ruled out. In this regard, it was stated that thyroxine polypeptide obtained by tryptic digestion of thyroglobulin is more active calorigenically than either L-thyroxine or D-L-thyroxine (41). Following administration of therapeutic doses of I^{131} , only half of the protein-bound I^{131} was butanol-soluble and identical with thyroxine, whereas the other half was not butanol-soluble and presumably was a larger molecule containing thyroxine (42). The large molecule was probably ejected from the damaged thyroid.

A word about terminology seems in order, since there are now too many symbols and synonyms for protein-bound iodine. First of all, the term "protein-bound" receives undue emphasis. By weight, the serum contains 1,000,000 parts protein to 1 part thyroxine, assuming that, under normal conditions, the protein-bound iodine is mainly thyroxine. With such a ratio, precipitation of the protein by one or another method would carry along by absorption a considerable quantity of free thyroxine. Furthermore, thyroxine being an ampholyte and also extremely insoluble in acid media, would be fairly well precipitated from aqueous solution in the absence of any protein by those same reagents employed in the determination of precipitable, protein-bound iodine. For these reasons and in the absence of data showing the binding by protein of thyroxine, it seems that there is no compelling necessity to designate the organic iodine of blood as "protein-bound." The solubility of the organic iodine of the blood in butanol has been interpreted as breaking a loose type of protein binding. Yet it seems more reasonable that it is merely an expression of the high solubility coefficient of thyroxine in this solvent. Therefore, the most adequate term seems to be "organic iodine," and this will be used throughout this text.

Examination has been made of the various factors affecting the concen-

tration of organic iodine in the blood. It is to be recalled that the concentration of organic iodine in serum represents the difference between the amount of hormone secreted by the thyroid and the amount of hormone metabolized or excreted during the same interval of time. Changes in total plasma volume or extracellular space might conceivably affect the concentration of organic iodine in blood. Moreover, alteration in the rate of breakdown of thyroid hormone might affect its concentration just as much as alteration in the rate of secretion of hormone from the thyroid. It is interesting to note that exposure of rats to cold, which intensifies thyroidal activity, was followed by a lowering of the serum organic iodine. Thus, requirements for thyroid hormone are increased in face of a heightened secretion of thyroxine by the gland (43). In guinea pigs, organic iodine did not rise in early pregnancy nor did it reflect the increase in oxygen consumption which occurred late in pregnancy (44). In dogs, adrenalectomy produced a lowering of organic iodine in blood (45). Considerable work on the biometry of organic iodine has established standards of values within age and sex groups of man (46).

Many studies have demonstrated the usefulness of determining organic iodine concentration of blood for clinical purposes (47, 48). In the human, the normal value lies between 4 and 8 $\mu\text{g.}$ per 100 cc. of serum, and higher values are rarely encountered except in hyperthyroidism and during pregnancy (49). Low values appear in hypothyroidism and many other conditions. Various organic substances containing iodine produce a spurious increase of organic iodine. On the other hand, during the first day following administration of mercurial diuretics, analytic values for organic iodine concentration are markedly depressed (50) because of the interference of mercury in the estimation of iodine. The organic iodine of a newborn infant is the same as that of its mother within 12 hr. after birth, but up to one year of life it is slightly higher than in euthyroid nonpregnant adults (51). During the first 16 weeks of pregnancy, organic iodine is elevated and some relation exists between the failure of the organic iodine to become elevated during pregnancy and the incidence of abortions (52). Shortly after delivery, organic iodine values become normal. In schizophrenia, despite the characteristic low oxygen consumption and resistance to exogenous thyroxine, organic iodine values do not differ from those of normal persons (53).

Metabolism of thyroid hormone.—The metabolism of thyroxine has been studied in man (54) and animals (8), chiefly by means of radiothyroxine. Thyroxine space is 23 per cent of body weight in 6 hr., rising slowly to 33 per cent in 24 hr. After injection of radiothyroxine, the thyroid accumulates I^{131} at a slow constant rate which is independent of plasma concentration of thyroxine. Thus, the thyroidal I^{131} must have been due to radioiodide liberated by the catabolism of the thyroxine. Ten per cent of the urinary I^{131} behaved as thyroxine, the remainder as iodide. Eight to 14 per cent of the dose was eliminated in the feces. From these figures, it was calculated that one-third of the thyroxine iodine is removed per day. Radiiodotyrosine given intravenously to the human (55) had a very limited existence, the compound being deiodinated completely in about 6 hr. Approximately 200 cc. of serum

were thus cleared per minute of diiodotyrosine. A small proportion of diiodotyrosine appeared in the urine. No localization of radioactivity occurred in the body in contrast to the localization noted over the liver subsequent to injection of radiothyroxine. Excretion and distribution of both radiiodotyrosine and radiothyroxine have been studied in rats and compared with those of radioiodide (8). More than 80 per cent of radiothyroxine given was found in the urine and feces in 96 hr., a quite different excretion pattern from that noted after the administration of either radioiodide or radiiodotyrosine. Radiothyroxine was concentrated in the stomach, the small bowel, and liver, which indicates that thyroxine may undergo an enterohepatic circulation. Analysis of the radioactivity in tissues following the injection of radiothyroxine disclosed the presence, not only of thyroxine and iodide, but also of two unknown compounds (56).

ACTION OF THYROID HORMONE

On energy metabolism.—Thyroxine induced a rise in oxygen consumption in guinea pigs within 4 hr. (57). To the increased energy production fat contributed twice as much extra metabolism as other foodstuffs (58). The basal expenditure of energy was accelerated by thyroxine in dairy cows. Because of the extra food consumed, the cost of the extra milk obtained by feeding thyroprotein was twice that under normal conditions (59). Rectal temperatures of rams and rabbits were elevated by thyroxine, and lowered by thyroidectomy (60). The metabolic response to cold environment was found not to depend on a hyperthyroid state. Survival at low temperatures required the presence of thyroid hormone (61).

On growth and differentiation.—Rats thyroidectomized at birth were retarded in growth and differentiation; thyroxine reversed this effect (62). However, the growth rate of swine was not affected by thyroprotein (63). In hypophysectomized rats, thyroxine increased appetite, and body weight and length, but its most marked action was acceleration of skeletal maturation (64). The hastened maturation and differentiation of cartilage caused by thyroxine was studied in rats by means of S^{35} . No change or a lowered S^{35} deposition in the cartilage of the knee joint was noted (65). Stimulation of the ossification processes of long bones up to the marrow stage was induced by thyroxine in *Xenopus* tadpoles (66). Thyroid hormone added to tanks containing young *Lebistes* increased growth by 30 per cent in males and by 50 per cent in females. In hypothyroidism resulting from thiouracil, a decline of 20 per cent occurred in growth rate (67).

On intermediary metabolic processes.—In hyperthyroidism, the synthesis of *p*-aminohippuric acid was depressed to about two-thirds of normal (68). Thyroxine also inhibited glutamic acid oxidation by rat kidney cortex (69). The urinary excretion of pentose was augmented by thyroid hormone and diminished by thiouracil (70). The increase in urinary nitrogen occurring following burning of rats which have been in a cold environment was independent of thyroid (71). The rate of amino-acid catabolism was increased and the conversion of body protein to amino acids was depressed in fed or

fasted thyroidectomized rats (72). This was reversed by physiologic doses of thyroxine. In the eviscerated rat, thyroidectomy reduced the increment of plasma amino acid (73). Metabolic requirements for vitamin A were greatly increased in experimental hyperthyroidism in chicks (74). During thyroid therapy in myxedematous patients, the carotenemia was said to fall while the content of vitamin A of the blood rose concomitantly (75).

On liver and hematopoietic system.—The oxygen consumption of isolated muscle was accelerated 12 hr. after thyroxine administration, at which time neither liver nor kidneys had been affected (76). Therefore, the increase in metabolism of muscle induced by thyroxine did not require prior activation of the liver. However, the effect of thyroxine on the heart rate was enhanced after partial hepatectomy or after ligation of bile ducts, showing that the liver excreted or inactivated thyroid hormone (77). Thyroxine protected the liver of the mouse against central necrosis produced by carbon tetrachloride and chloroform (78). Hyperthyroidism accelerated and hypothyroidism retarded the exchange of P^{32} of adenosine triphosphate of liver (79). Thyroid reduced lactic dehydrogenase of rat liver (80). In view of earlier studies showing thyroid to be a lipotropic agent, it was found that the accumulation of cholesterol in the liver was as high in control rats fed a diet rich in cholesterol as in rats fed the same diet containing thyroid (81).

The marrow fat content was found to be decreased and cellularity increased in most hyperthyroid patients. In hypothyroidism, on the other hand, the fat content was normal but the marrow showed a marked hypoplasia of all cellular elements (82). The metabolism of pigeon bone marrow was repressed by thyroidectomy but curiously not affected by thiouracil (83). The oxygen consumption of erythrocytes of hyperthyroid patients was twice that of normal persons (84).

On cardiovascular system.—The oxygen consumption of atria and ventricles of hyperthyroid rats was 45 per cent and 23 per cent respectively greater than in normal rats (85). Since no difference between atrial and ventricular respiration was noted in euthyroid rats, it would appear that atria are more sensitive than ventricles to exogenous thyroidal materials. In hyperthyroidism, cardiac output was increased but hepatic and splanchnic blood flow remained normal. Only systolic blood pressure was elevated in the right ventricle and pulmonary artery (86).

On integumentary system.—Thyroid hormone induced a thickening of the derma in fish (87). A thinning in the cornified layers was observed in the rat (88). The fiber length of wool in male lambs is increased by mild hyperthyroidism (89). In cases of localized myxedema, an accumulation of hyaluronic acid and large mast cells was found. It was postulated that mast cells secrete mucopolysaccharides which are characteristic of the localized myxedema (90).

On central nervous system.—The oxygen consumption of the cerebral cortex was not different in normal, hyperthyroid, or hypothyroid rats (91). The same seems true in man (92).

On endocrine system.—The extreme hypertrophy of the mouse pituitary

following large doses of I^{131} has been reinvestigated. Since this hypertrophy was inhibited by 3 μ g. thyroxine per day, it was felt that the pituitary enlarged as a consequence of the hypothyroid state induced by irradiation destruction of the thyroid (93). The administration of thyroid to normal human subjects resulted in a marked suppression of endogenous thyroidal activity as measured by the accumulation of radioiodine (94). This is presumably due to suppression of thyrotropin secretion. The same effect was produced by a functioning struma ovarii (95). Increasing doses of thyroid in hyperthyroid patients did not induce a marked depression of thyroidal I^{131} uptake (96). It would perhaps suggest that in hyperthyroidism, thyrotropin cannot be inhibited or that it is already inhibited to such an extent by the excessive thyroid hormone characteristic of this disease that further repression by exogenous thyroid substance is not possible. Thyrotropin was found to be absent from the serum of patients with pituitary insufficiency, markedly elevated in acromegaly, and low in thyrotoxicosis (97).

Thyroxine increased and thiouracil decreased the weight of the adrenals in male mice (98). The atrophy of the adrenal glands induced by thiouracil or by thyroidectomy was reversed by physiologic doses of thyroxine (99). Such atrophic adrenals responded normally to epinephrine or adrenocorticotrophic hormone (ACTH) (100, 101). To explain the atrophy, the suggestion was made that in the hypothyroid rat less ACTH is being elaborated when the pituitary is busily secreting excess thyrotropin (101). By a combination of tests for adrenocortical function, it was found that decreased adrenal reserve may be present in cases of severe human thyrotoxicosis (102). In myxedema, the excretion of 17-ketosteroids is low and is not corrected by adequate thyroid therapy. Adrenal activity concerned with metabolism of electrolytes seems to be normal in myxedema. No consistent defect of adrenal activity with regard to organic metabolism was observed (103).

The response of the comb of the fowl to androgen varies directly with the amount of thyroid secreted (104). In the female chick, however, thiouracil augmented the response of the oviduct to estrogen (105). Thyroid hormone decreased in rats but potentiated in mice the response of the ovaries to pregnant mare serum (106). In hypothyroidism induced by thiouracil, a heightened response of the ovaries to exogenous gonadotropin occurred. Spermatogenic activity (mouse, rabbit, ram) was stimulated by hyperthyroidism and reduced by hypothyroidism (107, 108). The ram also showed more Leydig cell function during experimental hyperthyroidism. Early maturity and ovulation occurred in hyperthyroid female mice, whereas in hypothyroidism ovulation was inhibited. It was felt that in hyperthyroid mice, the gonadotropic hormone secreted was mainly luteinizing while in hypothyroidism follicle-stimulating hormone predominated (109). Reproduction was still possible in rats kept goitrous for three to nine months. The estrous cycles were lengthened but implantation was not affected. Some resorption of the embryos occurred after the seventh day of pregnancy and gestation was slightly prolonged (110, 111). Contrary to previous work, thyroidectomy was without effect on pregnancy in the rabbit (112). Normal folliculogenesis,

heat, impregnation, normal development, and lactation were observed in hyperthyroid guinea pigs. Hypothyroid animals showed an incidence of 91 per cent fertile matings, and gestation was of normal length. Consequently, in the female guinea pig, reproduction is possible within a fairly wide range of thyroidal activity (113, 114). Similarly, sex drive was not influenced within a wide range of thyroidal function in the male guinea pig (115). The estrogen-induced lactation in goats was not augmented by thyroxine therapy (116). Abnormalities of ovarian function in human thyrotoxicosis and myxedema have been re-examined. While there was some variation, anovulatory cycles seemed to be the rule (117).

Antithyroxine compounds.—A series of papers dealing with the synthesis of halogenated acrylic acid analogues of thyroxine has shown that a combination of a phenolic skeleton, a halogen and a hydroxyl group is necessary for antithyroxine activity. Iodine in the 2, 4, 6 positions of the phenyl ring imparts thyroxine-inhibiting properties (118). In thyrotoxic rats, dibromotyrosine, a substance with disputed antithyroxine qualities, was observed to lower the basal metabolic rate and to ameliorate the induced toxicity (119). Thyrotoxic rats gain weight when fed liver. Whether the responsible liver factor is vitamin B₁₂ or not remains in doubt, since vitamin B₁₂ only partly restored the depressed growth rate of thyrotoxic rats while various impure supplements did so more completely (120, 121, 122, 123). Vitamin B₁₂ did not decrease the high basal metabolic rate induced by excess thyroid feeding, although it reduced the nitrogen loss (124).

ACTIONS ON THE THYROID GLAND

Thyrotropin.—The increase of thyroidal I¹³¹ collection induced by thyrotropin in hypophysectomized rats has been made the basis for a new assay procedure (125). Some calorogenic action of thyrotropin was observed even in thiouracilized animals (126). Thyrotropin administered to normal and hyperthyroid patients whose thyroids had previously been labeled with I¹³¹ increased the release of thyroid hormone (127, 128). Thyrotropin injected into patients with secondary myxedema increased the I¹³¹ collection as well as other indices of activity of the thyroid. No such action usually occurred in primary myxedema. These physiologic effects were proposed as a differential procedure in the diagnosis of these two types of hypothyroidism (129, 130).

ACTH and adrenal hormones.—ACTH and cortisone given alone did not affect the thyroidal collection of I¹³¹ in hypophysectomized rats, but inhibited the action of thyrotropin given concurrently (131). In normal or adrenalectomized rats, ACTH reduced the thyroidal accumulation of I¹³¹. This was attributed to an inhibitory action of ACTH on thyrotropin secretion (132). An exhaustive study of the effects of various adrenal steroids on the collection of I¹³¹ by the thyroid of the normal rat demonstrated that ACTH and cortisone were most effective in curbing I¹³¹ collection (133). These authors wisely did not postulate a mechanism for this action. This depressant effect of ACTH and cortisone has, however, been denied (134), but one cannot be certain that the experimental conditions were identical.

Many papers have appeared following the announcement (135) that cortisone induces a hypothyroid state (corticogenic hypothyroidism) in patients being treated for rheumatoid arthritis. Hypothyroidism was attributed to an inhibition of secretion of thyrotropin by the pituitary. The evidence appears somewhat conflicting and confusing, and may be open to other interpretations: (a) Cortisone appears to have a direct action on the basal metabolic rate (136), as indicated by its slight calorogenic action in untreated myxedema. Therefore, interpretation of the changes of basal metabolic rate as evidence of alteration of thyroid function is not easy. (b) ACTH or the stress of surgical procedures increased urinary I^{131} , thought to be the result of increased catabolism of thyroxine (137). Consequently, the peripheral utilization of thyroid hormone, which is difficult to measure, should be considered. (c) The reduced thyroid accumulation of I^{131} and the variably lowered organic iodine of the blood of euthyroid patients given cortisone (138, 139) cannot be accepted as overwhelming evidence for thyroidal inactivity without knowledge of possible alterations in volumes of diffusion spaces and renal clearance. (d) An intimate thyroid-adrenal relationship via regulation of thyrotropin secretion by adrenal hormones is supported by claims that the occurrence of thyrotoxicosis is extremely high in Addison's disease (140) and that uncomplicated Graves' disease is ameliorated by cortisone. Both claims are probably erroneous. (e) There seems to be much internal inconsistency and variability in the various indices of thyroidal function before and after therapy with ACTH and cortisone and some of the changes reported seem too small to be significant. (f) Doubt may be expressed concerning the existence of the clinical entity of "corticogenic hypothyroidism." It is possible that thyroid function is suppressed secondary to corticogenic inhibition of secretion of thyrotropin. The foregoing discussion signifies that the present evidence for this conclusion is insufficient.

Gonadal hormones.— I^{131} collection by the thyroid in normal rats was increased by testosterone, progesterone, and estrone, and decreased by pregnenolone (141). Testosterone propionate did not affect thyroid weight (142). In rats, estradiol was found to stimulate thyrotropic activity of the pituitary (143). The goitrogenic action of thiouracil is said to be inhibited by estrogen in rats but not in guinea pigs (144, 145). Vernal activation of thyroid in the male frog was not arrested by castration (146).

Vitamins.—Because of its antithyroxic activity the effect of vitamin B_{12} on the thyroid was investigated. In normal rats no effect on thyroidal function could be demonstrated (147). However, in thiouracilized rats vitamin B_{12} reduced the size of the goiter and produced a lowering of the I^{131} uptake (148). The latter experiments, however, could not be repeated (149). During a careful study of the effects of vitamin A on the size and functional capacity of several endocrine glands, it was noted that the thyroidal collection of I^{131} was lowered (150).

Central nervous system.—It has been thought that thyroidal function is altered in schizophrenia; but in an investigation by means of I^{131} collection and measurements of organic iodine, basal metabolic rate, and plasma cho-

lesterol, no disturbance could be discovered (151, 152). Furthermore, no changes in thyroidal function were noted after insulin shock, electroshock, or combined shock and psychotherapy. Thyroidal function did not deviate from normality in patients with anxiety (153), or hypertension (154), or after prefrontal lobotomy (155). Electroshock evoked hyperemia and apparently increased functional capacity of the thyroid gland of the puppy (156), a finding similar to that obtained earlier in other animals.

Miscellaneous actions.—Late in tourniquet shock in rats, a reversible disturbance occurred in the I^{131} collection (157). Various types of stress (anoxia, nephrectomy, sham operations, starvation, and vitamin deficiency) suppressed thyroidal collection of I^{131} , the greatest effect being observed in anoxia (158, 159). High temperatures reduced the secretion rate of hormone from the thyroid (160).

Antithyroid substances.—Knowledge of the comparative physiology of antithyroid compounds seems to be slowly progressing. These compounds are active in turtles (161) and frogs (162), but for some reason not in certain elasmobranchs (163). The thyroid of the rat becomes refractory to thiouracil sometime during the sixth to ninth month, resulting in the reappearance of a fairly normal gland (164). An iodinated antithyroid compound, 5-iodo-thiouracil, has received considerable investigation (165). It depressed the metabolic rate, blocked I^{131} uptake in chicks and rats, produced a less hyperplastic gland, and did not, like thiouracil, potentiate the effect of thyrotropin. Further investigation of such compounds may lead to new knowledge of the interaction between goitrogens and iodine. The potentiation of thyrotropin by goitrogens first noted in normal chicks has been confirmed in hypophysectomized rats (166). Potentiation of thyrotropin is likewise shown by the enhanced secretion of thyroidal I^{131} in thiouracilized, hypophysectomized rats injected with thyrotropin (14). That goitrogens such as thiourea are concentrated thirty fold in the thyroid has been shown by use of thiourea containing S^{35} . Sulfur is oxidized to sulfate within the thyroid, and it was thought that this saturates the oxidative capacity of the gland for iodide (167).

New types of antithyroid compounds continue to appear. 2-Thiohydantoin activated the thyroid histologically but the iodine content of the gland remained unchanged (168). Compounds related to resorcinol were discovered to have antithyroid activity (169). Amphenone "B" produced a fourfold increase in the weight of the thyroid after 15 days of treatment and a tenfold increase after three months. This effect was absent in hypophysectomized animals, from which fact it was concluded that the mechanism of thyroidal enlargement must be the same as that evoked by thiouracil (170).

THYROID PHYSIOLOGY IN RELATION TO MEDICINE

Endemic goiter.—A fascinating story of the relation between nutrition and endemic goiter is well worth reading. In it is recounted the work leading to the isolation from rutabaga of a goitrogen, 1-5-vinyl-2-thiooxazolidone (171).

Thyroid cancer.—In the field of thyroid cancer most of the emphasis is

being placed on therapy with radioactive iodine and on various maneuvers to intensify the avidity of neoplastic thyroid for I^{131} . One-and-a-half years after the administration of I^{131} , neoplastic changes in the thyroid of the rat were detected (172). Similar changes have not been found in mice (173). Small doses of radioiodine increased the incidence of thyroid adenomas in rats given methylthiouracil but not in those given acetaminofluorene (174). A very interesting study of the behavior of human thyroid tumors when transplanted to the anterior chamber of the guinea pig eye has been performed. Almost every type of histologic pattern of carcinoma of the human thyroid may be seen during the survival of the transplant (175).

Hypothyroidism.—Some 27 hr. after a tracer dose of I^{131} , administration of potassium thiocyanate ejected the thyroidal radioiodine in cretinous children (176). In normal subjects, potassium thiocyanate will not discharge I^{131} unless it is given within an hour or so following the tracer dose. Thus the defect in cretinism involves the biochemical mechanism in the thyroid which binds iodine organically. The intracellular and interfibrillar substance in the cutaneous connective tissues in localized myxedema is thought to be mostly hyaluronic acid, and is reduced by hyaluronidase administered locally (177).

Hyperthyroidism.—The literature on hyperthyroidism consists chiefly of clinical trials with antithyroid drugs and radioiodine. A psychosomatic theory (178) of the etiology of thyrotoxicosis has been proposed: that increased social and psychologic demands lead to liberation of pituitary thyrotropin which causes thyrotoxicosis. However, the consensus is that the release of thyrotropin is curtailed in thyrotoxicosis. The problem of exophthalmos, one of the signs of Graves' disease, has been carefully reviewed (179). In experimental exophthalmos, an increase in the intracellular ground substance, water, hyaluronic acid, and hexosamine of connective tissues was observed (180). Exophthalmos occurring during administration of antithyroid compounds has been noted in humans (181), rats, guinea pigs (182), and in a marine fish (183). The concept that the exophthalmos is due to thyrotropin seems to have become a fixed idea, and accepted as a fact. It should be noted, however, that only equivocal and circumstantial evidence supports this view.

Diagnostic tests of thyroidal function.—Intensive evaluation of diagnostic tests to determine the level of thyroid function in the human is being made, two summaries of which are recommended (184, 185). The problem is not that any of the tests with I^{131} will supplant other tests such as the determination of blood organic iodine or the basal metabolic rate. Clearly, these last two tests have different meanings and are useful in situations other than those revolving about the avidity of the thyroid for I^{131} . Rather the problem is to determine which of the various maneuvers with I^{131} gives the most discriminating diagnostic information that can be obtained routinely. The "conversion ratio" test (186), which determines how much of the I^{131} of the blood is protein-bound, requires two days and too large a dose of I^{131} . The thyroidal accumulation 1 hr. after intravenous I^{131} has the advantage of rapidity (187). Perhaps the most satisfactory measure of thyroid function would be an evaluation of the amount of hormone secreted per day. It is

possible that this might be estimated conveniently and rapidly were the thyroïdal clearance of I^{127} easily determined. In any case, further work and careful biometry of the various I^{131} tests seem necessary.

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REPRODUCTION¹

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A number of useful volumes have appeared during the year. *Steroids in Experimental and Clinical Practice* (1) contains the proceedings of the First American Conference on Steroids held in Cuernavaca, Mexico. The results of the Ciba Conference (London) on *Toxemias of Pregnancy, Human and Veterinary* was edited by John Hammond and others (2). Prunty contributed a chapter on gonadotrophins and steroid hormones to Bowes's *Modern Trends in Obstetrics and Gynecology* (3). Two practical books are Emmens' *Hormone Assay* (4), and the revised edition of Burns's *Biological Standardization* (5), the latter enriched by a chapter on "Statistical Methods" by D. J. Finney and one on "Bioassay of Chemotherapeutics" by L. G. Goodwin. Williams' *Text Book of Endocrinology* (6) contains a chapter on the testes by Scott and one on the ovaries by van S. Smith. Thirteen authors contributed to the section on the ovary, and seven to the section on the testes, to Soskin's *Progress in Clinical Endocrinology* (7). Volume II of *Progress in Gynecology* by Meigs & Sturgis (8) includes articles on the basic anatomy and physiology of the reproductive organs and hormones governing reproductive processes, as well as clinical and therapeutic phases. Among clinical books are Wilkins' *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence* (9), Stolz & Stolz's *Somatic Development of Adolescent Boys* (10), and Nieburgs' *Hormones in Clinical Practice* (10a). A very comprehensive monograph on the gonadotrophic and steroidal hormones and their physiological actions in the human female is that of Lewin & Spiegelhoff (11). Reynolds' well-known *Physiology of the Uterus* (12) has been rewritten and enlarged. Endocrine influences in fetal development are covered by Moore's monograph (13). Ford & Beach have published *Patterns of Sexual Behavior* (14).

SEX CYCLES

Endocrine glands as they affect hibernation and the temperature mechanism, as well as the circulatory mechanism of arousal (16), have been analyzed (15). Nutritional factors (17) have much to do with seasonal rhythm of activity of the sex organs in the field mouse (18, 19). If estrous ferrets are desired, apply two parts or more of light to one of dark (20). In the junco, constant day-length induces growth of testes, though breeding cannot be maintained indefinitely (21). Testosterone aids increase of daylight in inducing testicular growth (22). In the drake, light rays of 366 to 546 m μ wavelength cause stimulation of the gonads; those of 574 to 836 of equivalent

¹ The survey of the literature pertaining to this review was concluded in late June, 1951.

light energy are negative (23). Darkness favors retention of pituitary gonadotropes (24), though the testes are still responsive (25). The peak in birth of calves in England and Wales is December to January, the trough June to July (26). Robinson has written a review of reproduction in the ewe (27). Gilts born earlier in spring tend to be more mature, though younger, than those born later (28). Congenital malformations of the central nervous system in man occur in 1.91 per 1,000 in May and in 3.09 per 1,000 in December (29). As the guinea pig matures, the duration of vaginal opening decreases from 6.3 days at puberty until stabilized after the fourth or fifth estrus at about 3.6 days (30). Removal of the pineal gland results in acceleration of puberty and massive luteinization of the ovaries in the rat (31), while the thymus extract (highly purified) delayed the onset of first heat and lengthening of estrous cycles in the guinea pig (32). Trum (33) records 1,543 cycles in the mare and determined the time of ovulation (mode: penultimate day of estrus). The male guinea pig copulates before he is able to ejaculate and ejaculates before he is fertile (34). Persistent estrus produced in rats by hypothalamic lesions can be changed to anestrus with progesterone (35). The pattern of egg laying in turkeys differs from that in hens (36), 60 per cent laying after noon (37). Oysters mature earlier and grow faster in the warm waters of Louisiana than their kin in Chesapeake Bay (38).

Menstruation.—Corner (39) and Goldzieher & Gilbert (40) published reviews on the subject of menstruation. The threshold for the production of uterine bleeding in spayed monkeys for progesterone alone (without pretreatment with estrogen) is 5 mg. per day for 21 days (41). Prostigmin₉ in causing menstruation-like bleeding in amenorrheic women probably acts via the diencephalon (42, 43), while folic acid antagonist (aminopterin) produces bleeding by interfering with the action of estrogen (44). Basal body temperature (BBT) readings have found their place in clinical diagnosis (45, 46, 47); it helps to determine the incidence of anovulatory cycles (48). In correlating BBT, stage of corpus luteum, and endometrial biopsy, Buxton & Engle (49) have found a discrepancy of four days in determining the day of ovulation in women. Normal women undergo cyclic changes in endogenous testosterone metabolism not of adrenal origin (50); elimination of the steroids are also subject to cyclic variation (51, 52, 53). Cyclic changes are recorded for blood lipids (54), serum protein concentration (55), and in skin reactions to progesterone and histamine (56). The level of blood progesterone in the menstrual cycle of the monkey is biphasic; first rise in mid-cycle, second larger rise in luteal phase (56a).

Somatic influences on reproduction.—Swine reproduce well on synthetic diets (57). The younger children of large families are the more likely to be sterile as adults because of juvenile malnutrition (58). Genetically obese mice are sexually underdeveloped and sterile [Speirs (59)]. The city rat (wild Norway) is more fertile than his less well-fed country cousin (60). In another study (61), heavier rats (on richer food) took longer to conceive. Protozoa follow the same pattern; thus the rate of reproduction of a Suctorian is de-

creased when a rich and abundant supply of food (*Tetrahymena*) is available (62). Effects of inanition on endocrine organs are compared with those of hypophysectomy (63). Castration aggravates the involutionary effects of inanition in the oviducts of toads (64, 65). The androgenic "X-zone" in the mouse adrenal is markedly reduced with a dietary regimen deficient in protein (66). Inanition renders accessory genital organs of castrated mice less responsive to steroidal hormones (67). Specific vitamin lack may or may not interfere with normal activity of the reproductive organs; thus, the female is more susceptible to folic acid antagonist than the male (68). Testis atrophy follows in the wake of phenylalanine, methionine, and threonine deficiency (via hypophysis) (69); but absence of tyrosine has no effect (70). Vitamin B₁ deficiency is accompanied by reduction of fructose and citric acid in male accessories, as in general B deficiency; but quantitative caloric restriction, with full B₁, also drastically reduces fructose and citric acid (71). Desoxypyridoxine added to diet had only slightly adverse effect except in pregnancy (72); pyridoxine deficiency and restricted caloric intake have similar effects in inhibiting testosterone action (73). Vitamin E was compared in its action to progesterone (74). Biotin deficiency is linked with cryptorchidism, possibly a result of tetany of the cremaster (75). Estrogen increases magnesium/calcium ratio in uterine muscle (76) but does not hasten calcium replenishment in the body (77). Magnesium is indispensable to reproduction in the rat (78). Mares have higher serum iron than stallions; castration lowers it (79). Boars are as fertile in restricted environment as when kept in a roomy paddock (80). Infection (81), brain injury (82), ultrasonics (83) may change the estrous cycle; 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane (DDT) disturbs reproduction and is cumulative (84). Excess cholesterol injures the testes (85); aminopterin (86), and cigarette smoke (87) do the same. Tompkins (88) makes a plea for more intensive study of effect of drugs on reproduction.

THE FEMALE GAMETES

Ovulation.—The relation of the hypothalamus to the anterior pituitary (AP) continues to be investigated. The nervous connections between these parts are described (89). Cycles in the rat continue after a two- to three-week interval following electrocautery of the base of the third ventricle (90). Ovulation is brought about in the estrous rabbit by electric stimulation at the right point, but not during pregnancy or in pseudopregnancy (91). The cyclic "4:00 P.M." ovulation in the rat [which is induced by luteinizing hormone (LH) release] may be inhibited by autonomic blocking agents (92, 93, 94); but these drugs do not affect ovulation in the rabbit induced by human chorionic gonadotropins in pregnancy urine (PU) or by pregnant mare serum (PMS) (95). Procaine prevents the decidual reaction in the rabbit (96), and atypical results are attained with gonadotropes after extirpation of the cervical sympathetic ganglia (97, 98). Knaus's brochure on the fertile period of the menstrual cycle has appeared in English (99). His conclusions

find some corroboration in practice [Doring, 526 cases analyzed (100)]. Other workers have correlated the various "signs" of ovulation (101, 102) without finding the Knausian precision as to time of ovulation, 15 days before onset of menses (103). The BBT is generally regarded as a valuable adjunct in diagnosis (104). In pregnancy, the BBT drops in spite of high titer of progesterone (105). The Farris method of measuring ovulation time by assaying urinary gonadotropin holds also for the monkey (106). Emotional states may affect ovulation (107), as in rape cases during the Russian invasion of Germany (108). The postparturitional ovulation in mice occurs at night; this happens regardless of whether the time of parturition is the day or the night (108a). Ovulation can be brought about by use of progesterone [rabbit (109); monkey (110)], or hastened by progesterone in women (111); and also in heifers (112). Superovulation in cattle by gonadotropes is discussed in the symposium edited by Vogtburg (113) [see also (114, 115, 116)]. For ovulation to be provoked in the toad by a single toad pituitary placed in the abdominal cavity, the ovary of the recipient must be exposed to the diffusing hormone for 3 hr. (117). In March the threshold is one-sixth of a pituitary for 3 hr., in December one-quarter for 4 hr. (118).

The ovary.—Taylor *et al.*, preliminary to extensive survey of structures in the human ovary, describe the apparatus used in the analysis of sections and the statistical treatment of measurements (119). Authors find histological evidence of postpubertal oögenesis in rat (120); but by meticulous counting of ova in normal and atretic follicles in rat (121), it is concluded that there can be no oögenesis after maturity. X-rays stop desoxyribonucleic acid (DNA) synthesis in germ cells and cause conversion of DNA to ribonucleic acid (RNA) (122). Ovaries transplanted into seminal vesicles give evidence of secretion of androgens (123). Evidence is submitted indicating that the theca interna is the source of androgens (124), but also of estrogens (125). By unilateral severance of nerves to the ovary it was discovered that they enter the ovary with the blood vessels (126). Ovarian vein pressures were studied (127) and found to be 14.5 mm. Hg with the subject lying down. The connective tissue of the human ovary undergoes changes with the menstrual cycle (128). The structure of lagomorph ovaries differs with the species (129). Just before ovulation the granulosa of the sow's ovary becomes folded (130), as in the bitch. Strassmann reiterates his contention for the existence of a "thecal cone," supposed to guide the ovarian follicle to the surface (131); but Arey considers the thecal cone nonexistent (132). A follicle (rabbit) may dehiscence within the substance of the ovary (133). Cyclic changes in size of nuclei in granulosa cells are less marked in *Ericulus* than in rat or man (134). Theca and stroma cells possess fluorescent granules, which are not endocrine in nature, however, but are blood pigment degradation products (135). Cytoplasmic inclusions in interstitial cells of the rat ovary are under the influence of gonadotropes (136). Cyclic changes in certain cell inclusions believed to be steroidal in nature are described for the sow's ovaries (136a). The pregnant cow's ovary contains 9.63 $\mu\text{g.}$ of iodine per

gm. of fresh tissue, which seems concerned with follicular activity (137). It is now possible to observe the human ovary *in vivo* by culdoscopy (138). *Zootoca vivipara*, a viviparous lizard, develops a true corpus luteum (139).

Ova.—The problem of transfer of ova from one individual to another is discussed (113). In the same symposium, Pincus describes the development of superovulated cow ova *in vivo* and *in vitro*, and Hammond states that two-celled ova go on to form blastocysts in 48 hr. *in vitro*. Chang (113, 140) reviewed the problem of mammalian egg transplantation. He describes cleavage (fragmentation) (except for one egg with haploid chromosome number?) of unfertilized ferret ova (141). Mouse eggs undergo differentiation, forming trophoblast, when implanted under the capsule of the kidney (142). Casida and his group at Wisconsin successfully transplanted an eight-celled cow egg into a favorable recipient which carried the resulting fetus to term (gestation 278 days). No "foster mother" influence was seen in the calf (143). New studies relate to cytochemistry of ova: Jones-Seaton published a monograph on RNA in rodent eggs (144). Alfert made photometric determinations of DNA in ova after Feulgen, paralleling measurements of tyrosine and tryptophan (145). DNA doubles with cleavage, not with growth of the ovum. Microinjections of human chorionic gonadotropins into rabbit follicle (0.00005 I.U.) cause formation of first polar body (146). In the hen, the first polar body is given off 2½ hr. before laying (147). Gametes of sea urchin injured with ultraviolet light may be reactivated with visible light (148) (cf. bacteria). A biochemical study was made of mucopolysaccharides in the albumen-layer of amphibian eggs (149).

THE MALE GAMETES—SPERMATOZOA

The Golgi apparatus is responsible for acrosome and headcap of human sperms (150). Lipids, polysaccharides, and phosphatases have been demonstrated in human sperm (151), and 17 amino acids have been recovered from bovine sperms (152). At 32°C. the rate of beating of the sperm tail was seen to be about the same as that of cilia: 14 to 16 per sec. (153). Drugs which attack the sulphydryl group stop sperm motility, cysteine, and glutathione protect against the action of such drugs (154). In a half billion *Paracentrotus* sperm per ml. there is 0.00690 mg. glutathione; in 3 billion per ml. 0.03288 mg. (155). Glycine prolongs fertilizing capacity of sea-urchin sperm (156). Rate of fructolysis is proportionate to sperm concentration (157). Fructose in rabbit semen is variable; testosterone increases it, estrogen inhibits it (158). In man, fructose in semen is independent of quality of sperms (159). Maltose is slowly glycolyzed by bull sperms (160). The *Journal of Dairy Science* and *Poultry Science* has carried articles on semen diluters or "extenders" for artificial insemination (q.v.). Sperms differ according to species in surviving rapid freezing (161). Hyaluronidase can be extracted from human testes and from seminal fluid (162, 163), but the latter produces no estrogenic response in castrated female rats (164). What constitutes normal semen is variously discussed for man (165), cattle (166, 167), and the thoroughbred

(168). Sperm concentration may be determined by light transmission (169). Sperm counts in men vary from day to day (170). The Farris method of evaluating motility of sperms (171) is the most exact (172). Rate of reduction of methylene blue by sperms in capillary tubes is a handy measure of their metabolism (173). Various staining methods are employed to distinguish dead sperms in a given sample (174 to 178). Killed sperms added to a sample of live sperm do not affect motility or fertility of the latter (179). A set of monozygotic triplet bulls were found identical in sex responsiveness and in semen quality (180).

Semen quality was determined and analyzed in 1,000 cases of infertility in each of two studies (181, 182), and, for the first time, semen quality of 1,000 men of known fertility was analyzed. The latter were compared with 1,000 men in infertile marriages (183), 800 of whom were analyzed as to sperm number (184). Human sperms live longest in cervical mucus about ovulation time (185), and those that reach the cervix are seen to be morphologically the more perfect (186). The rate of travel of sperm from cervix to ampulla of tube in man is higher than has been supposed, requiring only 30 min. (187). Very few sperm reach the ovum; many arrive gradually long after the ovum is fertilized (188, 189). The Parker theory of sperm transport is accepted as the most reasonable postulate (190). Mayer again brought up the old idea that the husband's semen is of physiological value to the wife; as the author admits, the essay consists mostly of hypothesis (191).

FERTILIZATION

Mann edited a symposium on fertilization (192), and Chang & Pincus (193) and Moricard (194) wrote reviews on physiology of fertilization in mammals. A popular summary is that of Monroy (195). Moricard attributes previous failure of fertilization of mammalian eggs *in vivo* to excess oxygen and attained partial anaerobiosis by culturing mouse ova and spermatozoa in an isolated loop of the oviduct. Result: fertilization, "semi *in vitro*" (196). Direct observation of fertilization of ova was accomplished by various biologists. Dan (197) saw sperm entry and "surging" of the cytoplasm in medusan ova and sperm entry in Echinoderm eggs (198). Pasteels (199) observed rhythmic pulsation around the fertilization cone in eggs of marine Annelids. Every step in the process of fertilization in the rat from entrance of sperm to cleavage stages has been demonstrated by phase microscopy by Odor & Blandau (200). Fertilization occurred despite close adherence of cumulus cells, also observed by others (201, 202), indicating that hyaluronidase is not needed to denude the ovum (203). Sperms themselves carry hyaluronidase (204). Chicken eggs fertilized by stale sperm are likely to produce embryos with abnormal central nervous system (205). Ova secured from ten-day-old pseudopregnant rabbits by gonadotrope injection, fertilized by sperm injection in utero, are largely lost because of pyometra. Such fertilized eggs, however, removed and transplanted into noninfected pseudopregnant does, develop normally (206). For pregnancy to continue after such

transplantation, it is essential that the stage of the recipient uterus (pseudo-pregnant at the time) correspond exactly in point of time to the stage of development of the eggs (207, 208).

Pregnancy.—Maintenance of pregnancy was attacked by a new method: Virgin does (no corpora lutea!) received one-day-old fertile "albino" eggs in one tube, and five days later six-day-old vesicles in the opposite tube; 35 mg. progesterone, plus implantation of a progesterone pellet, maintained pregnancy to term, but maternal instinct was generally poor post partum (209).

Fertility and sterility.—Articles on this subject abound in *Fertility and Sterility*, Volumes 1 and 2, and in Volumes 19 and 20 of the Belgian veterinary journal, *Vlaams Diergeneesk Tijdschrift*.

RELAXIN

A new assay method and relaxin unit is suggested: measuring spread of pubic bones of guinea pig in x-ray photographs with legs spread by 500-gm. weights (210). A method of mounting the animal and placing photographic film with reference to source of x-rays is described (211). Relaxin can maintain the state of relaxation for only a short time (212). As to sources of relaxin: per gram of tissue, ovaries gave 25 to 30 guinea pig units, placenta 50 to 75, uterus 10 (213). Relaxin has a molecular weight of 9,000, and is a low molecular weight protein or polypeptide (214). It has been shown that 1.5 μ g. per day for 8 to 20 days brings about relaxation; 1.0 mg. per day progesterone has no effect, inhibits action of estrogen (215, 216). Therefore, since women sometimes suffer pain because of shift of pubic bones (217), it is suggested that progesterone be prescribed to remove the cause rather than prescribing analgesics (218). Lack of vitamin C does not interfere with the action of relaxin (219, 220). Acetylcholine relaxes the symphysis of guinea pig primed with estrogen, more especially in the female (221). Prostigmine has a similar influence in pregnant women (222). Biochemical changes in the pubic ligament are being studied (223); estrogen raises the water content, calcium is increased by 100 per cent, phosphorus lessened by 40 per cent, phosphatase increased (224), although phosphatase as well as hyaluronidase are said to play no important part in the relaxation (225). The theory is expressed that increased tone of skeletal muscles plays a role in estrogen-induced relaxation (226).

FEMALE ACCESSORY ORGANS

The uterus.—The course of smooth muscle fibers of the uterus and changes in shape and arrangement during contraction have been reinvestigated (227). Nerve fibers extend into the basal layer of the endometrium, but there are no ganglion cells in the uterine wall (228). In two-thirds of 790 cases the volumetric capacity of the human nulliparous uterus ranged between 1.4 and 1.8 cc.; the maximum was 3 cc. (229). The physiological significance of changes in the vascular pattern of the extraplacental uterine mucosa of the

rabbit was pointed out (230). Attempt was made to explain the variations and time overlap of proliferative and secretory phases of the human endometrial cycle (231). That the castoff menstrual endometrium is viable is confirmed (232). Alkaline phosphatase is abundant in the proliferative, scarce in the secretory phase of the human endometrium (233). The lucid basal zone of the rat uterine mucosal cells, not usually mentioned, is not made up of glycogen but probably of lipid (234). Fat is deposited in gland cells, beginning at the age of fifteen days; deposition is hastened by various steroids (235). Tissue mast cells accumulate in cotyledons of virgin bovine uteri at maturity (236). Nucleoproteins are most abundant in the late proliferative stage of the human endometrium, the increase being entirely due to RNA (237).

By photometric techniques applied to single nuclei, it was found that, regardless of size, nuclei contain identical amounts of DNA, but that non-chromosomal protein is proportionate to size (238). Water, electrolytes, nucleoproteins, and residual phosphorus are affected by estrogens (239). No increase in water at the beginning of the secretory phase was to be noted in human endometrium (240). Compounds having affinity for the -SH group interfere with estrogen-induced growth of the uterus (241). Vascularity, uterine growth, and myometrial activity are closely bound to the contractile actomyosin and the noncontractile myosin (242). Actomyosin decreases after castration, and is restored by estrogen (243); it rises during pregnancy, and at parturition is high in corpus uteri (244). Estradiol increases phosphorus turnover (P^{32} used) of uterine but not of skeletal muscle (245). Vasopressin rather than oxytocin causes contraction of the uterus, and it does this at all times of the menstrual cycle and in early pregnancy (246, 247). Progesterone rather than estrogen sensitizes the uterus to respond to pituitrin (247, 248), for the response is absent in anovulatory cycles and is the greater the higher the titer of urinary pregnandiol (249). Relaxation of guinea pig and rabbit uteri *in situ* is affected by intravenous injection of aqueous extract of corpus luteum (250). The growth of the human myometrium was studied by count of mitoses in muscle cells (251). In tissue cultures of myometrial cells, blood from pregnant women increased rate of proliferation (252). Norepinephrine would seem to be the "sympathin" of uterine muscle, content in ovarian vein rising from 0.005 to 0.037 $\mu\text{g. per ml.}$ on stimulation of hypogastric nerve (253).

Cervix uteri.—The human endocervix is reported to exhibit no cyclic histological changes (254). Squamous metaplasia of cervical mucosa is normal in pregnancy and not precancerous (255, 256); it may also be associated with endometrial hyperplasia, but other factors than estrogen are necessary for development of carcinoma (257). There is little if any cyclic change in galactose, mannose, fructose, or hexosamine in cervical mucus (258), nor in glucose or maltose (259). Diastase is present (259). On incubation, 16 to 32 per cent of reducing sugars disappear (260), and on addition of one million sperm to 100 mg. mucus, utilization of sugars is doubled (261). Seventeen

amino acids have been identified in cervical mucus; they decrease in mid-cycle (262). Lipids make up 2.9 per cent of dry, 0.082 per cent of wet mucus (263). The pH, read with glass electrode or Hydriion paper, varies from 4.0 to 9.0, lowest near the external os (264). The osmotic pressure is the same as blood (265). Viscosity of mucus and BBT are lowest in mid-cycle (266). Characteristics of crystallization on drying vary with the viscosity of mucus (267). Rheological studies show that in cows the flow elasticity of the cervical mucus is always maximal at estrus; but in women this stage in the mucus occurs at greatly variable times of the menstrual cycle (268). In the cow the viscosity fluctuates greatly, but rises gradually in pregnancy (269).

Vagina.—The comprehensive volume of de Allende & Orios (270) on exfoliate vaginal cytology (without cancer diagnosis) has appeared in English. The volume by Pundel (271) includes the cervix and diagnosis of cancer. Shorr's review (272) of clinical application of the vaginal smear method should prove useful, as should Fitoussi & Crepeaux's well-illustrated article (273). The method (274) has found world-wide use both in cancer detection and in control of hormone therapeutics. Not only may cervical and uterine carcinoma be detected early, but also uncommon neoplasms from higher up (275), from the oviduct (276), and from the ovary (277). As there is a close correlation between extent of cornification and estrogen dosage (278), vaginal response may readily be gauged by the physician. A plea is made for more meticulous analysis of the smear (279) and statistical treatment of cell counts: activity index = c/p , where c = cornification, p = pycnosis (280). New classification of menopausal cell types are suggested (281). The effect of intrauterine radium on ovarian activity may be determined (282), and threatened abortion diagnosed (283, 284). The *post partum* return to normal may be followed by the vaginal smear studies (285). The value of glycogen stains is problematic (286, 287). Betaglucuronidase in vaginal lumen is correlated with cornification and leucocyte number (288). Cells in urinary sediment have diagnostic value (289). The vaginal smear is not always a mirror of functional state of endometrium (290, 291, 292). Jaworski made a detailed study (highly illustrated) of vaginal cytology in the rat (293). Special attention given to leucocytes in the rat (294) revealed preponderance of mononucleocytes (295). Progesterone potentiates estrogen in causing cornification in the guinea pig (296). Lactic acid in the rat vagina is highest in mid-estrus (297). Wislocki showed that intercellular bridges of oral and vaginal squamous epithelium are integral parts of cells (298). Riehm gave especial attention to the connective tissue of the vaginal wall (299).

ENZYMATIC PROCESSES IN REPRODUCTION²

Intermediary metabolic processes in reproductive physiology have not been investigated as much as might have been expected from earlier stimulating reports on variations in some enzyme systems. However, the publica-

² Contributed by Dr. N. Millman, Ortho Research Foundation, Raritan, New Jersey.

tions described below indicate a rising trend in that direction; the more rapid development of such investigation may come within the near future.

The alkaline phosphatase of the cervical mucosa is at a minimum during menses, but at maximum during estrogenic phases. No enzyme was present during the menopause (300). Ovariectomy decreases the amount in uterus and vagina where it may be restored with estrone (301). Relaxation of the symphysis pubis of the guinea pig appears to be proportional to the degree of alkaline phosphatase activity of the pubic ligaments (302). It has also been suggested that the enzyme plays a role in epithelial metaplasia (303). An enzymatic flow chart of reactions leading to fructose accumulation in accessory male organs emphasizes the importance of phosphatase reactions (304).

The development of the prostate during adolescence can be followed by the excretion of acid phosphatase in the urine (305). Substances giving such activity may be extracted and purified from the human ejaculate, and it appears that there may be more than one acid phosphatase in semen. The perfused prostate was used to indicate that the hydrolysis of phosphorylated intermediates is due to naturally occurring acid phosphatase of the gland itself (306). The administration of estrogens to male guinea pigs decreases the acid phosphatase, while the total amount of alkaline phosphatase remains the same, but shifts from epithelium to stroma and muscle (307). A medico-legal test has been established on the basis of this enzyme in seminal stains, independent of the presence of sperm (308).

The ability of tissue homogenates to convert 3-phosphoglycerate to phosphoenolpyruvate through the enzymes phosphoglyceromutase and enolase has been demonstrated in testis, ovary, and uterus. In other tissues, the female has significantly lesser conversion ability than the male (309). Furthermore this ability is decreased in males given stilbestrol, in females given estrogen, and in both sexes following cortisone or ACTH. Particularly noteworthy for its implications for sex differences in the metabolic cycle is the report that ovariectomy increased the rate of formation of phosphopyruvate, while castration decreased the rate in the male (310).

Succinic dehydrogenase in the seminal vesicle and prostate of the rat is decreased by castration; the same is true of malic dehydrogenase. Lactic acid content of these organs is increased fourfold. The administration of testosterone restores the enzyme levels to normal (311). However, in striated muscle there is no change upon castration or androgen treatment (312). The pigeon crop gland increases in succinic dehydrogenase activity after lactogenic hormone stimulation (313). It may be noted that x-irradiation inhibits citric acid synthesis in the testis of fluoroacetic acid-treated rats (314).

Amino acids have an important effect on the metabolism of sea-urchin spermatozoa; upon addition to sea water they cause an increase in total oxygen used, in functional life span, and in duration of motility and fertilizing capacity, even though sperm cells do not seem to metabolize these amino acids (315). A peptidase, which splits L-leucylglycine, is present in the pubic

ligament of the guinea pig, but its concentration is not proportional to the degree of relaxation of the pubic symphysis (302). The antichymotrypsin content of serum may be abnormally increased after the fifteenth week of pregnancy (316) in almost 50 per cent of cases.

There is no cyclical change in β -glucuronidase activity of rat uterus (317) although a decrease does occur a few days after ovariectomy, and this may be overcome by administration of estrogens (301, 318). The same is true of vaginal tissue (301). In the uterus of the nine-day pseudopregnant rat, levels are lower while the deciduomata have higher activity than the control uterus. An increased activity is also noted with growth of the uterus, while the highly stimulated prostate and seminal vesicle exhibit no increase in enzyme over castrated controls (319).

In vitro tests of placental and kidney histaminase show a potentiation in the presence of estrogens, but an inhibition with chorionic gonadotropins (320). Kidney D-amino oxidase may also be inhibited by sodium estrogen sulfates and by desoxycorticosterone, perhaps by reaction with the apoenzyme (321). An enzyme which converts to Δ^5 -3-hydroxysteroids to unsaturated α,β -ketones has been found in liver (322) and in endocrine tissue (323).

Other publications have described the purification and properties of a 5-nucleotidase in bull seminal plasma (324), the decrease in placental glutaminase towards the end of pregnancy (325), and the similarity of chondroitinase of testis to hyaluronidase (326).

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THE PHYSIOLOGY OF THE SKIN¹

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Although certain aspects of skin physiology have been reviewed recently, this is the first general review on this subject since 1946. There has been so much excellent research pertaining to the physiology of the skin since that time that all of it cannot be covered in the space allotted. In limiting the coverage of the material we have selected important and interesting contributions which have emphasized developmental, structural, and functional mechanisms.

SEBACEOUS GLANDS, SEBUM, SKIN LIPIDS

The lipids on the surface of the skin are a composite of sebaceous gland secretion (sebum), the lipid content of the surface epithelial cells, and any changes of these which may be due to microbiological activity or to some other enzymatic action. In their histochemical observations of the sebaceous glands of the rat, Montagna & Noback (1) postulated that the peripheral acinar cells of the gland contain phospholipids; the larger, more centrally placed acinar cells contain large quantities of unsaturated glycerides; and the mature dying acinar cells, which are about to undergo or are undergoing sebaceous degeneration, contain large quantities of unsaturated glycerides and cholesterol esters. The sebum is composed primarily of unsaturated glycerides and cholesterol esters. The alkaline phosphatase activity was also abundant in the acini, the peripheral cells containing a greater concentration of the enzyme than the central cells. Ribonucleic acid, though present in those peripheral acinar cells which possess few or no lipid droplets, is not present in the mature acinar cells and sebum.

Parnell's studies (2) on the functional histology of sebaceous glands in the same animal (rat) revealed that sebaceous cells seem to be replaced both from mitosis of cells in the periphery of the gland (slow rate) and from the stratum germinativum and deeper layers of the duct wall (accelerated rate). In postnatal development the sebaceous gland undergoes a definite cycle: (a) sebaceous cells are added slowly and dermal fat increases (to 17 days of age); (b) the sebaceous cell enlarges and fills with sebum at the expense of the dermal fat (18 to 27 days of age); (c) these sebum-filled cells disappear in the secretory phase; and (d) the stratum germinativum is activated and

¹ The survey of the literature pertaining to this review was concluded in July, 1951.

sebaceous cells, lost in the secretion, are replaced rapidly from deeper layers of the duct wall (28 to 31 days of age). This sebaceous gland cycle is correlated with the hair cycle, the resting period of the hair coinciding with the active phase of the gland (filling and secretion). This cycle is dependent upon the metabolism of the skin, and it can be accelerated by irritation and retarded by castration. Methylcholanthrene is capable of completely destroying the sebaceous glands in the skin of the mouse four days after one local application [Montagna & Chase (3)]. If the follicles contain growing hair, sebaceous glands begin to differentiate anew from the cells of the external root sheath. In follicles where hair bulbs are not yet growing, the sebaceous glands will not regenerate until growth of the bulb is underway.

Evidence continues to accumulate that the size and activity (but not the number) of the sebaceous glands can be increased with androgen stimulation [Ebling (4), Montagna & Hamilton (5)]. In such androgen-stimulated skin, mitotic activity occurs in the peripheral cells of the sebaceous acini and is not confined to the cells in the epithelium of the sebaceous ducts—Montagna & Kenyon (6)]. The flow of sebum from the gland and duct is not a function of the autonomic nervous system in the same sense as eccrine sweat glands secretion. If the hair is pulled, the sebum maintains a constant, but low level on the skin surface (2). Accumulation of sebum on the skin surface is largely controlled by viscosity of the sebaceous layer and so is altered by temperature. The viscosity largely affords the resistance to further exudation of sebum from the gland orifice, thereby regulating the accumulation of sebum on the skin surface [Butcher & Parnell (7,8), Dunner (9), Butcher & Coonin (10)]. The specific gravity of sebum collected from human foreheads has been found to be 0.911. The surface tension (26.5° to 31°C.) averages 24.89 dynes per cm. The viscosity at 38°C. was 551.9 millipoises, at 30°C. was 859.7 millipoises, and at 28.5°C. was 984.3 millipoises. Sebum separated into various components when the temperature was lowered to 29°–30°C. and ceased to flow at 15° to 17°C. (10).

In humans the rate of secretion of sebum does not seem to be influenced by soap and water washing, the local application of astringents (aluminum chloride) (11), or the oral administration of biotin (12). The quantity of lipids on the skin surface correlates well with the size of skin pores. In women a fair correlation was found between the lipid secretion, greasiness, thickness, and turgor of the skin [Kvorning & Kirk (13)]. There is also a correlation of the amount of lipids and age—a small secretion in childhood increasing gradually at puberty, greatest in the adult years, and decreasing in the aged [Kvorning (14)]. Herrmann & Prose (15) found a relatively consistent amount of ether-soluble substances at a given site in the same individual; however, various consistent differences existed in symmetrical and different areas of the body surface. They also indicate an enhancing effect sweating on the quantity of the ether-soluble film on the skin surface. According to Kvorning (16), the surface skin lipids of the forehead are composed of about 50 per cent triglycerides, 10 to 20 per cent esters of higher

alcohols (among them is a small amount of cholesterol), and an even larger amount of fatty acids. Phosphatids were not present to any considerable extent. At the hair line (7) of an individual with good hair and a small amount of dandruff, the average amount of skin lipid was 0.114 mg. per sq. cm., 8.6 per cent of which was cholesterol; an individual with oily scalp and sparse hair had more lipid (0.163 mg. per sq. cm.), of which 7 per cent was cholesterol; and an individual with much dandruff and thin hair had 0.145 mg. of lipid per sq. cm., of which 10 per cent was cholesterol. The total surface lipids also increased with acne, but the cholesterol content did not change [Kile, Snyder & Haelele (17)]. Squalene has recently been found to be a general constituent of sebum [Sobel (18)].

Rothman and his co-workers (19) carried out extensive chemical analyses of human hair fat in adults and children in an attempt to understand the spontaneous cure in puberty of *Microsporon audouinii* infections of the scalp (tinea capitis). The total fat comprised 3.6 per cent (by weight) of the hair. The free fatty acids equaled 6.6 per cent of the total fat. These investigators attributed the strongly fungicidal properties of adult human hair to the saturated fatty acids, which have a straight chain arrangement and have only odd numbers of carbon atoms 7—9—11—or 13 in the chain. They make up about 2 per cent of total hair fat. Except for formic and propionic acid, this fat of human hair is, at present, the only known source of naturally occurring monobasic normal aliphatic acids having odd numbers of carbon atoms.

ECCRINE SWEAT GLANDS

List (20) recently reviewed the physiology of sweating. The material covered by him will not be included in this report. In the past, sweat gland function was studied as it pertained to water and electrolyte balance, metabolism, nutrition, body temperature, acclimatization, etc., for the body as a whole. In recent years more attention is being focused on the physiology of the sweat gland as a secreting unit. It is well accepted that cholinergic drugs, introduced locally into the skin by injection or by ion transfer, can excite eccrine sweat glands. The reports of Kadatz (21), Kisin (22), Gibson & Shelley (23), Janowitz & Grossman (24), Issekutz, Hetényi & Diosy (25), and Shelley & Horvath (26) add further evidence to this.

Recently the question has been raised as to the existence of an adrenergic component in the nervous mechanism of human eccrine sweat glands. Haimovici (27) induced moderate sweating after intravenous injections of Neo-Synephrine (phenylephrine hydrochloride) and blocked this effect as well as spontaneous palmar sweating with Dibenamine (N,N-dibenzyl- β -chloroethylamine), an adrenergic blocking agent. Kisin (22) and Sonnenschein (28) produced local sweating by local injection of epinephrine. The latter (28) could not alter the response by atropine or tetraethyl ammonium chloride, but could diminish it with procaine and inhibit it by Dibenamine. Wada (29) also stimulated the sweat glands with intradermally injected epinephrine. By establishing the "minimal effective concentration," he was

able to show a lower excitability of the sweat glands to epinephrine in children 1 to 12 years of age and in adults 62 to 77 years of age; the highest excitability in both sexes was reached at 14 years. Interestingly, the sweat glands of the newborns (one week old) had the same excitability to epinephrine as their puerperal mothers.

Haimovici (30) also suggests that sympathin E and the excitatory component of epinephrine are responsible for the sudomotor ability of the adrenergic systems, and that both cholinergic and adrenergic agents exert a synergistic sudomotor action. Sonnenschein (31) and his co-workers take exception to such opinions. Although the evidence of their more recent work supports the contention that the sweat glands respond directly to epinephrine, they feel that the existence and function of an adrenergic innervation of human eccrine sweat glands is not proven. The problem is not yet settled. There seems no doubt that the cat possesses no adrenergic component to its sudomotor innervation [Patton (32)].

Two reports deal with the segmental effect of pressure or pain on sweating. Korr (33) demonstrated low electrical skin resistance areas, segmental in distribution, associated with clinical or experimentally produced pain. Clinical improvement was accompanied by elevation of the skin resistance and a shrinking of the low-resistance areas. Takagi & Sakurai (34) demonstrated that pressure on one side of the body evoked hemihidrosis on the opposite side and pressure on the soles or hip evokes the upper and lower sweating reflex. According to McGregor (35), when skin is grafted from a thermal sweating area to a palmar skin area, the skin graft retains its anatomical sweating pattern, but acquires the physiological sweating pattern of the recipient site.

Randall & McClure (36, 37) demonstrated that the preliminary response of the sweat mechanism to mild exercise was an increasing number of functioning glands. As the stimulus to sweating became stronger, there was an increased output by individual glands. In addition, they demonstrated that sweat glands do not act continuously, but periodically discharge sweat upon the surface of the skin when the subject is resting quietly in a warm environment. Such periodicity or pulsatile sweat secretions were measured by an infrared gas analyzer by Albert & Palmes (38). At low sweat rates such pulses appear in bursts. At moderate rates they occur continuously with an average frequency of 6 to 7 per min. At very high rates, both frequency and amplitude of the pulsations were dampened. Most of the active glands were discharged at the same time. Similar observations were made by direct skin microscopy of the portal openings of palmar sweat glands by Lobitz & Osterberg (39). Randall & McClure (36) were able to estimate that the average output of a "typical" sweat gland (at rest in a warm climate) from the arms and legs was 0.0037 to 0.0043 mg. per min., while from the dorsum of the hand and foot it was 0.002 to 0.003 mg. per min. [According to Burch (40), the threshold for such sweating of a normal man resting in bed is an environmental temperature of 34.4°C. and 50 per cent relative humidity.]

Marked differences in sweating rates were observed on different skin areas; thermal sweating appears first and most profusely on the calf and thigh, next on the lower trunk and forehead, and finally on the upper extremities (41, 42).

The chemical histology of the eccrine sweat gland has been studied by Bunting *et al.* (43) and correlated with the function of the sweat gland in animals by Sperling & Koppanyi (44) and in the human by Shelley & Mescon (45). The latter show that prolonged secretory activity of the sweat gland leads to complete disappearance of glycogen from the acinar cells. Fats, sulfhydryl groups, deoxyribonucleic acid, and alkaline and acid phosphatase, which are also present in these cells, are unaffected by secretory activity.

In an attempt to gain more information concerning the sweat secreting unit, Lobitz and his co-workers (39, 46 to 50) carried out "tolerance" studies for chloride, urea, glucose, uric acid, ammonia nitrogen, and creatinine on simultaneously collected sweat, blood, and urine. The sweat was collected directly from the openings of the sweat pores in capillary pipettes in order to avoid contamination in so far as possible with surface cells, sebum, etc. Their studies revealed that the palmar sweat glands will freely secrete urea when the urea in the blood is elevated (palmar sweat urea is always greater than blood urea), slowly secrete uric acid when the uric acid in the blood is elevated, quickly secrete creatinine when the levels in blood are elevated, effectively bar glucose from reaching the surface of the skin when the levels in the blood are elevated acutely or chronically, and effectively produce ammonia nitrogen. Their results suggest that the coil (acinar) portion of the gland might act as a selective secretor and that the duct, coil, or both, may reabsorb water from the sweat.

The interpretation of electrolyte concentrations in sweat is once again under discussion. Earlier reports correlated the chloride concentration of sweat with sweating rates, skin temperatures, acclimatization, etc. Recently Conn and his associates (51, 52, 53) point to the probability that the sweat electrolyte pattern can be used in clinical and experimental medicine as an indication of either diminished or excessive adrenal production of "salt-active" corticosteroids. The complicated process of metabolic acclimatization to heat is thought to be accomplished by increased secretory activity of adrenal cortices which in turn have been activated by pituitary adrenocorticotropin. The studies of Locke *et al.* (54) also suggest that the chief determinant of their "sweat chloride-rate index" values is an adrenal cortical hormone which acts chiefly upon electrolyte and water metabolism. However, they also show that under conditions of a constant hormonal status, sweat electrolyte composition is influenced by nonendocrine factors related to thermal stimulus, skin temperature, and rate of sweating. Robinson *et al.* (55) show that the reduction of chloride concentration in sweat with acclimatization depends upon the development of chloride deficiency due to excessive salt loss in the sweat.

It is difficult to interpret reports on the various chemical constituents of sweat. Sweat that is contaminated with epithelial cells, surface oils, bacteria, etc., will yield different results from sweat that is filtered, cleared, or collected so as to avoid these contaminants [cf. Adams *et al.* (56) with Mitchell & Hamilton (57)]. Heir, Cornbleet & Bergeim (58) report the microbiological determination of 10 free amino acids in sweat. These do not appear as a result of filtration from blood plasma and are not important in the amino acid economy of the body. Lactic acid concentration, which in the sweat may be as high as 300 mg. per cent in the preacclimatized state, settles down to about 100 mg. per cent during acclimatization. Weiner & Heyningen (59) wonder if the glycogen known to be present in the acinar cells of sweat glands is a precursor of lactic acid in the sweat.

KERATIN

Giroud & Leblond [(60); see also Mercer (61)] in their x-ray diffraction and histochemical studies show that the sulfur of the epidermis and its derivatives is mostly present as cysteine residues in the malpighian layer, while cystine resides in the cornified layer. At the limit between these two zones, the oxidation of cysteine into cystine probably provides cross links between the individual polypeptide chains making up the tonofibrils, thus transforming the keratin precursor of the tonofibrils of the malpighian layer into the completed keratin of the tonofibrils of the cornified layer. This is one mechanism by which the strength and chemical inertness of keratin may be explained. Block (62) indicates that the "hard" keratin proteins (hair, nails, etc.), called eukeratin, are heterogeneous, but (in contrast to many other homologous tissue proteins) show a wider range in their pattern of the majority of their amino acid components, and a remarkable constancy in the molecular ratios of histidine to lysine to arginine. Evidence is also produced [Bolliger (63)] that many of the nonkeratinous constituents of hair are derived from nucleic acid present mainly in those epidermal nuclei which disappear in the process of keratinization. The rate of growth of "hard" keratin structures (nails, hair, etc.) may be measured by estimating their increase in length; the soft keratin structures, such as epidermis, cannot be so measured since there is desquamation of the cornified cells as they reach the surface [Storey & Leblond (64)].

HAIR

There are multiple aspects to the consideration of the physiology of hair growth in animals and man (65)². Chase & Montagna (66) point out the importance of knowing the phase of the hair growth cycle in the interpretation of damage induced in mouse skin. In the developmental cycle of a hair follicle the anagen stage (17 days) is the phase of active growth and development [Chase *et al.* (67) have observed six clearly defined substages in the anagen

² The reader is referred to the recent report of the Conference on "The Growth, Replacement, and Types of Hair" (65).

phase]. The catagen stage (2 days) is the phase of growth cessation, club hair formation, and the setting aside of the dormant hair germ for the next hair generation. The telogen stage is the resting phase. X-radiation (300 r to 1000 r), for example, in the anagen phase results in cessation of development in the follicle and loss of any growing hair. No such hair loss occurs during the catagen or telogen stages. In contrast, repeated applications of irritants, such as K_2PO_4 , ether, benzene, or methylcholanthrene-in-benzene, have no effect on hairs in the anagen, but cause loss of hair in the telogen stage. Pigment loss for the ensuing hair generations is greatest in follicles x-rayed in the catagen or telogen stage (66). Investigations from the biochemical and histochemical aspects by Flesch & Goldstone (68, 69) indicate that the depilatory action of such agents as the intermediary polymers of chloroprene and naturally occurring squalene is one of epidermal sulfhydryl inhibition. Flesch (70) also presents more evidence that dark hair contains more cystine than light hair.

Both alkaline phosphatase and glycogen are present in the primitive hair bud [Johnson & Bevelander (71)]. On elongation, phosphatase disappears while glycogen remains abundant. Phosphatase makes its appearance in the mesenchymal components of hair as soon as they are elaborated. The density of the capillary bed [Durward & Rudall (72)] about the hair follicles varies according to the stage of the hair growth cycle. The distribution of capillaries is similar to that of alkaline phosphatase activity. The body skin of embryonic mice produced normal hair follicles and hairs when cultivated *in vitro* by Hardy (73). Interestingly, denervation of an area of skin has no effect on the passage of the wave of hair growth over it. In the rat, Baker (74) found that growth is retarded of both hair and other parts of the body in states of hypothyroidism, hyperthyroidism, hypopituitarism, and hyperadrenocorticism, and is a reflection of general metabolic actions. However, two reactions stand out that seem to place the responsiveness of hair in a unique category: (a) the acceleration in rate of hair growth that follows adrenalectomy, regardless of the physical condition of the animal; (b) the extensive growth of hair, even though at a reduced rate, in the hypophysectomized rat while the level of proliferation of other parts of the body is very low.

In the human [Myers & Hamilton (75)] the average number of days required for regeneration of 90 per cent of the follicles from which hair was plucked was: 129 in the crown of the scalp, 123 in the axilla, 121 in the thigh, 117 in the area of the scalp above the ear, 92 in the chin, and 64 in the eyebrow. The slow rate of regeneration in scalp hairs occurred in all age groups. Scalp hair regenerated more rapidly in males than females, but the reverse occurred in the axillae and thighs. The rate of growth of hair is fastest for the long hairs (chin 0.38 mm. per day, and scalp 0.35 mm. per day) and slower for the short hairs (axilla 0.30 mm. per day, thigh 0.20 mm. per day, and eyebrow 0.16 mm. per day). It is the long hairs with the fastest growth that require the longest intervals for regeneration. The rate of growth of the scalp hairs is faster in females than males, while the reverse is so in

the axilla. Hamilton (76) places great significance on the quantitation (weight and growth rate) of axillary hair in the human as a measurement of secondary sex characteristics. Such quantitative measurements bear a general relationship to titres of urinary ketosteroids and androgens; axillary hair growth is produced ordinarily by secretions of the ovaries and testes and not to any large extent by secretions of the adrenal cortices.

In interpreting the significance of the types and distribution of hair in man, Garn (77) indicates the importance of a proper classification for any given study. Hair types can be classified morphologically as to gross size, time of appearance, and structural variations (six types); morphologically they can also be classed on the qualitative and quantitative differences in hormones needed either to "trigger" or to maintain their growth (three types). Body hair distribution can be classified as to location, pattern, and density. In devising a rating system for body hair, Garn divides the body surface in 11 significant regions and takes into account the presence, absence, and amount of hair in each region. In evaluating his data, he points out that the method of stating the frequency of body hair on each region is most suited for racial comparisons; the method of expressing the total number of areas bearing terminal hair may be satisfactory for females and for relatively glabrous races, but is not satisfactory for males; the method of summing up the total amount of hair by regions, for all regions, gives the most satisfactory result for this particular study of hirsutism in white men.

MELANIN

Although it is not within the scope of this review to discuss the various enzyme systems of the skin, recent work on the biochemistry of melanin formation should be reported. At the time of the last review, the presence of tyrosinase had not been conclusively demonstrated in mammalian tissue. Lerner & Fitzpatrick and their group (78) recently obtained mammalian tyrosinase from the Harding-Passey mouse melanoma and showed its activities to be the same as dopa-oxidase. This mammalian tyrosinase, a copper protein, catalyzed the slow oxidation of tyrosine to dopa and the fast oxidation of dopa to the intermediate products (dopa-quinone, etc.) in the formation of melanin. They also showed that although the oxidation by tyrosinase to dopa is initially slow, it becomes markedly accelerated by small amounts of dopa.

CUTANEOUS VASCULAR PHYSIOLOGY

Various investigators have used the temperature of the skin as a measure of blood flow. Martinez & Visscher (80) recorded skin temperature of nine normal subjects exposed to local heating while maintained in a constant environment at a cold temperature. They observed that local heating by immersion in water at 43°-44° C. produced a greater rise in skin temperatures (except the back) when the two forearms were immersed than when the legs were immersed. Immersion of one leg alone did not produce a significant

general skin temperature rise. The authors postulated that if cutaneous temperature changes reflect alterations in blood flow through surface tissues, then prolonged vasodilatation which follows local heating is probably mediated by some type of central mechanism. However, in earlier studies Lewis demonstrated that the temperature of the skin is a valid measure of blood flow in an extremity only under certain conditions. Fetcher *et al.* (79) emphasized this observation. In instances where direct measure of blood flow is not feasible and skin temperature is used instead, the part of the body under investigation must lose heat at a rate of more than 240 kcal. per hr. per sq. m. for good correspondence between blood flow and skin temperature changes. The effects of various amino acids on peripheral blood flow and skin temperature were studied by Macht (81). Values for skin and rectal temperatures, total oxygen consumption, and blood flow through the hand were obtained from four healthy males before and after ingestion of various amino acids. Five of the seven amino acids caused a definite increase in oxygen consumption; no consistent quantitative relationship between total oxygen consumption and skin temperature, or total oxygen consumption and peripheral blood flow were demonstrated. In studies of the cutaneous temperature of the extremities in patients with rheumatoid arthritis, Martin *et al.* (82) observed an inability of these patients to conserve body heat by means of prompt constriction of cutaneous vessels of the hands and feet. Generalized heating of the body resulted in a more prolonged vasodilatation in the hands and feet than did local applications of heat. Moist and dry heat had essentially the same effect on the cutaneous temperature of the extremities.

Greenwood *et al.* (83) attempted to study quantitatively the tone of cutaneous vessels. They applied a weighted ring to the forearm, and by observing the ring of hyperemia and measuring the time required for skin color to return to normal found this method of rough value in detecting the tone of cutaneous vessels. Interesting observations on the relations between cutaneous blood flow and blood content in the finger pad, forearm, and forehead were reported by Hertzman *et al.* (84). With use of a photoelectric plethysmograph they demonstrated that the relative value of the ratio of volume change to flow change may be employed as a measure of change in venous tone. Their data showed that the total quantity of blood in the cutaneous circulation is relatively small.

Ray (85) has described a technique for the estimation of oxygen supply to the skin. He observed the spectral changes in light reflected from interosseous skin before and after sudden occlusion of the circulation. The time for the spectral change is referred to as the reduction time, and ranged between 35 and 40 sec. in the normal patient. The reaction appears to be related not only to oxygen supply and its utilization, but also to the time for approximate capillary stasis to occur. In another study Ray, Ray & Johnson (86) discussed factors that influence reduction time of blood in skin capillaries. They observed that the reduction time was correlated positively with al-

veolar oxygen tension and systolic and diastolic blood pressures, and negatively with basal metabolic rate. In this study they observed that a period of breath holding maintained to a point of discomfort produced in normal subjects a decrease in reduction time. This may have been due to a change in the factors reported above.

In studies on skin temperature and circulation in decompression sickness, Tobias *et al.* (87) found that a variation in the circulation in the extremities was an important factor in the development of decompression sickness. Those with significantly lower hand temperatures developed bends pain. The subjects studied made simulated ascents to 35,000 feet at room temperature. Heated suits slightly decreased the incidence of severe bends.

In a series of experiments using microtechnique, McMaster (88, 89) demonstrated a slight pressure gradient between the interstitial fluid and the lymph in the normal skin of mice in over one-half of the cases investigated. This gradient was increased when edema was induced by xylol or heat in spite of the accompanying increase in intralymphatic pressure. He feels that this pressure gradient is an important factor in lymph formation. Using the same technique McMaster studied the effect of venous obstruction on the interstitial intradermal pressure in limbs of mice and human beings. The interstitial pressure increased over sixfold in a period of about 20 min. after obstruction, and thereafter remained constant. This indicated that at this point the interstitial pressure balanced the capillary pressure sufficiently to prevent further escape of capillary fluid.

SENSATION, METABOLISM

Further support of the theory that histamine may be the mediator for cutaneous pain is given by studies of Rosenthal (90). He observed an immediate and latent painful sensation when histamine was injected into the superficial layers of the skin of human subjects. The intensity and duration of the pain were found to be proportional to the concentration of histamine, and the interval between the primary and latent secondary response was inversely proportional to its concentration.

Kernwein (91) studied the recovery of sensation in split thickness grafts. He found that recovery was partial and patchy and usually appeared between the seventh and ninth postoperative week. Absence of underlying scar tissue and an intact nerve supply in the recipient area were reported to be essential for recovery. Urbach & Lentz (92) in their studies of sugar content of human skin found that the content was about one and one-half times that of the blood. A low carbohydrate diet resulted in a reduction of skin sugar content to a greater extent than blood sugar content; a high fat diet reduced skin sugar content without affecting blood sugar levels. In studies on the metabolism of skin, Barron *et al.* (93) determined that anaerobic glycolysis was two times as great in the fetal human skin as in the adult skin, whereas respiration was about the same. Agents were demonstrated to inhibit glycolysis much more than respiration, indicating that glucose metabo-

lism in skin may proceed through other pathways than glycolysis. Citrate and α -keto-glutarate were not oxidized while pyruvate and succinate were oxidized, suggesting an alternative pathway of metabolism through the succinate-fumarate system. Inhibition of respiration and glycolysis in the skin of rats by mustard gas and lewisite was demonstrated. The immediate effect of mustard gas was found to be inhibition of glycolysis rather than respiration. British antilewisite (BAL) increased glycolysis in the normal skin and partially restored glycolysis in mustard treated skin, reportedly by reactivation of oxidized sulfhydryl enzymes. Inhibition of respiration and glycolysis, owing to the inhibition of sulfhydryl enzymes by lewisite, was reversed by the addition of BAL at a ratio of lewisite to BAL of 1 to 5.

ABSORPTION

Seeberg (94) demonstrated that intradermal absorption was generally accelerated in skin showing toxic and allergic reactions. He also found a correspondence between the response to intradermal injection of allergic and toxic substances and the rapidity with which they were absorbed. In further studies (95), using the decrease in radioactivity of intradermally injected radioactive phosphorus and the Aldrich-McClure technique as a means of estimating speed of skin absorption, he showed that skin absorption and skin reactivity varied cyclically with menstruation. In contrast with the above study, skin absorption was greatest when reactivity was least. Percutaneous absorption of a variety of drugs into the clipped skin of rabbits using various vehicles was studied by Luduena *et al.* (96). Absorption was demonstrated for epinephrine, penicillin, and choline esters when these substances were dissolved in diethylene glycol monoethyl ether and other vehicles, but the dosage required for systemic effects was high and absorption was irregular. No epidermal absorption could be demonstrated for insulin, penicillin, or dihydro- β -erythroidine.

Experiments *in vivo* on guinea pigs by Clark (97) demonstrated the efficacy of polyethylene glycols ("Carbowaxes") as vehicles in promoting absorption of sulfonamides into injured skin, particularly when the "Carbowax" was used in pure form rather than combined with oil or water bases. The type of vehicle made little difference in normal skin, but in injured skin penetration was greatly increased with all vehicles, and particularly with pure "Carbowax." Skin levels were not appreciably increased by applications of over 1 hr. or concentrations of greater than 10 per cent.

Laug *et al.* (98), using the chemical assay of mercury in the kidneys as a measure of its cutaneous absorption in experimental animals, found that absorption was reduced by removing excess ointment from the skin and was greatly increased by covering the innunction site. Of no effect was the location of the innunction site or washing the skin prior to innunction. The authors (99) found absorption of lead oleate, acetate, and arsenate to be extremely small, and the absorption of lead tetraethyl to be relatively great. Mechanical injury to the skin was found to increase absorption in accordance

with Clark's (97) experiments. Further evidence that skin injury facilitates absorption is furnished by Lange & Evans (100) who found cutaneous absorption of radon, as measured by the radon content and the volume of expired air, to be doubled in a patient with leg ulcers as compared with a subject with intact skin.

Columbine (101) showed by a histochemical technique that free mustard gas exists only in the epidermis once penetration has occurred. This indicated that in order for therapeutic agents to be effective in preventing skin damage, they must block the fixation of mustard gas rather than merely react with free mustard gas. In later studies with mustard gas and lewisite, he (102) showed that the skin reaction is enhanced by wetting the skin or defatting it with xylol, and reduced by prophylactic application of fat or by induced sweating.

Burch & Winsor (103) studied the rate of diffusion of water through dead skin from various portions of the body. They found diffusion to occur most rapidly through skin of the palms and soles, moderately rapidly through the skin of the axilla, and least rapidly through the skin of the epigastrium. Using radioactive sodium tracers, Ussing (104) studied the transport of sodium through isolated frog skin separating two salt solutions. He found sodium influx to be consistently higher than outflux, in spite of low concentrations of sodium chloride on the outside. Chloride influx paralleled but as a rule was lower than sodium influx. Sodium influx rose when the pH of the inside solution was increased or when the potential difference between the two solutions was increased. Epinephrine added to the inside of the skin caused a violent drop in potential difference, an enormous increase in sodium outflux, and a considerable increase in sodium influx.

HORMONES

Baker & Whitaker (105) applied adrenal cortical preparations to the skin of rats and observed atrophy of the epidermis and inhibition of growth of hair follicles. When adrenocorticotropin was administered parenterally (106) to adult male rats, there occurred thinning of the epidermis, reduced growth of hair, and inconsistent reduction in the size of sebaceous glands, increased compactness of the dermal connective tissue, and reduction in the panniculus adiposus. This effect occurred with a dosage of 3 mgm. a day for a period of 21 days.

The percutaneous application (107) of estrone in alcohol to hirsute subjects did not affect hair growth or sebaceous activity. However massive doses of estradiol benzoate caused atrophy of the sebaceous glands in the female rat (108). Testosterone propionate given in dosage of 1 mg. daily increased the size and activity but not the number of sebaceous glands. Bullough (109) found that continued administration of estrogenic substances in mice reduced the mitotic activity of the hair bulb. When estrone was injected every 12 hours for three days starting on the first day of diestrus, the mouse epidermis reached a maximum thickness after two injections but

decreased rapidly from then on. The author concluded that mitotic activity and epidermal thickness are increased by estrogenic substances whereas prolonged use causes the opposite effect.

Baker & Whitaker (111) produced suppression of hair growth by administering estrogen to oophorectomized rats. However, estrogen administered to oophorectomized-adrenalectomized animals failed to suppress hair growth, demonstrating that the inhibitory action of estrogen on hair growth is dependent upon the integrity of the adrenal cortex.

Dieke (110) tried to determine whether the waves of hair growth (called hair cycles) of Norway rats were under endocrine control. She found that thyroidectomy or hypophysectomy caused cycles of abnormal pattern and slowness; adrenalectomy resulted in accelerated cycles of normal pattern, and gonadectomy had no effect on hair cycles. The above studies indicate that hair growth may be inhibited by adrenal cortical extracts if given parenterally or percutaneously, and by estrogen only if administered parenterally for fairly short periods of time in an animal with an intact adrenal cortex. Dieke's work suggests that there may be tonic suppression of hair growth by the adrenals but not by the ovaries. The effect of adrenal cortical extracts on epidermal thickness seems to parallel the effect on hair growth, both of which are suppressed. In contrast to this, estrogen causes skin atrophy only after an initial increase in thickness. Sebaceous glands are reduced in size by parenterally administered adrenal cortical extracts or massive parenteral (but not percutaneous) doses of estrogenic substances, and are increased in size by parenterally administered testosterone without apparent effect on their number.

NUTRITION

Further light is shed on the possibility that water soluble nutrients may be lost in the sweat under hot moist environmental conditions by the studies of Spector *et al.* (112). They measured 5.1 μg . per hour dermal excretion of pantothenic acid in subjects on an unsupplemented diet under comfortable environmental conditions, and 27.7 μg . per hour when the environmental temperature and humidity was increased. An increase was also noted in the urinary excretion of this vitamin. However, Johnson *et al.* (113) concluded from their work on the excretion of nicotinic acid and its metabolites in the sweat and urine that the amounts of these substances present in sweat are too small for profuse sweating to influence the nicotinic acid requirement.

Two authors have reported on the dermatological sequelae of malnutrition. Chavarria (114) noted alopecia and canities in infants and children of Costa Rica with severe vitamin deficiencies. These changes were reversed if an adequate diet or vitamin therapy were given. The authors believe that biotin supplements accelerate the return to normal. Nicholls (115) described four children of age 5 to 12 in a dark-haired race whose head hair, eyebrows, and fine hair had all become white, without change in texture. All had multiple vitamin deficiencies. In one case a good diet was instituted, and within three weeks pigment began to return in the hair.

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